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**Technology Assessment in Healthcare:
Beyond Current Practice in Lombardy Region**

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Executive Summary

The increasingly attention to proper allocation of scarce economical resources, and the necessity of managing a flourishing market of new technologies in healthcare, imply the search of the most efficient and beneficial solutions; this is even more evident in a national context of *spending review*, where recent regulations imposed mechanisms for widespread revision and rationalization of public spending in the attempt of avoiding reduction of service level. Consequently, Health Technology Assessment (HTA) has emerged as an important tool for supporting the core functions of an effective healthcare system, as its four main features are (Cicchetti, 2008):

- health policy orientation,
- interdisciplinary content and process,
- use of different methodologies of analysis, including methods for results' synthesis,
- emphasis on dissemination and communication of results achieved.

Given these basic components, good governance can rely on HTA to provide a policy approach that is accountable for its decisions to the population, and for this reason organizations specializing in health technology assessment are becoming institutionalized elements of health systems, not only to help identify healthcare interventions that may not be effective, but also to identify promising technologies that can stimulate innovation (WHO, 2011). In Italy, for instance, the approach for management of technology innovation in healthcare is not still widespread and well institutionalized in the National Health Service (in Italian, Servizio Sanitario Nazionale – SSN); however, recently HTA has been appreciated also at institutional level as a beneficial help for promoting the introduction of appropriate innovation and strongly encouraging a cultural attitude towards the appropriateness of interventions.

Following these considerations, the boundaries of the present research were defined by converging on a macro-objective, which is referred to the necessity of properly institutionalizing the Lombardy Region VTS-HTA (Valutazione delle Tecnologie Sanitarie – Health Technology Assessment) process at large scale, as the first Italian structured example which enables well-reasoned decision making; thus, this main target was declined in the following three research questions:

- RQ1: Is the current architecture of the VTS-HTA model properly legitimized?
- RQ2: Is the current process efficient in order to guarantee a straightforward and transparent functioning from the perspectives of exchanges of information and organizational structure?
- RQ3: What are the main levers driving an effective improvement of both design and management structure of the process?

Answers to research questions were finally articulated in the form of proposed recommendations for process improvement, which could be directly presented to both regional VTS-HTA representatives and further international organizations which currently they collaborate with.

According to the literature review that was first performed to better deepen the research background, HTA could be defined as *“a multidisciplinary field of policy analysis. It studies the medical, social, ethical and economic implications of development, diffusion, and use of health technology”* (International Network of Agencies for Health Technology Assessment, 2002). Therefore, it behaves as a “bridge” between who develops knowledge and who makes investment choices, thanks to a multitier approach which supports decision making at different levels, such as individual or patient level, the level of healthcare provider or institution, or at the regional, national and international levels. As Health Technology Assessment considers a variety of impacts including the effectiveness, appropriateness and cost of technologies, it can be undertaken by different types of organizations, belonging both to the private and the public sector, and, depending on the scope of assessment, multiple types of experts are needed, such as (Goodman, 2004):

- Physicians, nurses, radiology and laboratory technicians and other clinicians and allied health professionals;
- Managers of hospitals, clinics and other healthcare institutions;
- Biomedical and clinical managers;
- Patients and patient affairs representatives;
- Economists, lawyers, social scientists, ethicists and decision scientists.

Thus, Evidence Based Medicine (EBM) and evaluation techniques are defined as pillars of the HTA discipline. Regarding the first concept, different stakeholders are involved to determine current best evidence from scientific and medical research, and then to apply clinical experience and observation in making decisions about healthcare of individual patients. Moreover, different methods have been elaborated to qualify and grade levels of evidence provided by distinct typologies of studies, such as the scale of the University of Oxford (Centre for Evidence Based Medicine – CEBM), or the ranking scheme described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Regarding the organizational structure of HTA, different models have been elaborated in years, with a higher or lower degree of integration and networking between health agencies which are increasingly moving towards different methods of involving patients’ and citizens’ perspectives, besides the clinical and economic dimensions.

The second basic concept of describing different models for economic evaluations in HTA was important since the theme of resource allocation showed to be dominant in almost all industrialized

countries, in parallel with the increasing healthcare needs expressed by the population. Hence, three categories of costs, to be taken into account in economic analyses, were identified: first, costs of resources consumed in the healthcare sector, costs of patient's and his relatives' resources, and finally costs of other sectors' resources, for example the voluntary work, or areas related to the general economic context of a certain country. Therefore, the most used methodologies for analyzing costs are three: in the cost-benefit analysis (CBA), both costs and consequences of compared alternatives are expressed in monetary terms; on the other hand, in the cost-effectiveness analysis (CEA) the evaluation of benefits is based on non monetary units of measurement, providing results in terms of "cost per effectiveness unit", which is the incremental cost/effectiveness ratio of compared programs (ICER). Lastly, the cost-utility analysis (CUA) measures the expression of benefits and the utility gained from the state of health, represented in terms of QALYs (Quality Adjusted Life Years), which is an indicator representing weighted life expectancy thanks to the program/treatment implemented.

These prerequisites were meaningful for better understanding the basic foundations of international experiences which developed different frameworks of analysis in years: the National Institute for Health and Clinical Excellence (NICE), which was established in England and Wales, defined a three-tiered procedure for HTA distinct in phases of scoping, assessment and appraisal. On the other hand, the European Network for HTA (EUnetHTA) developed both a structured information framework and network to spread health decision making models and support policy decisions, namely the HTA Core Model. In addition, the Canadian EVIDEM Collaboration (Evidence and Value: Impact on Decision Making) elaborated a framework aimed at helping HTA and efficient healthcare decision making with a tool which facilitates the systematic and explicit consideration of multiple factors that may influence decisions, the Multi-Criteria Decision Analysis (MCDA). A further investigation about this decision making method was undertaken with a search on the database SciVerse Scopus, which highlighted its features from the organizational perspective: MCDA is a methodological approach which embraces different relative points of view, by defining relevant and exhaustive criteria which characterize decision makers preferences; thanks to the allocation of weights and scores to each criterion, their weighted sum identifies a MCDA Index which can be then employed for final priority setting of healthcare technologies. A second method named Programme Budgeting and Marginal Analysis (PBMA) was also examined, since it was developed for specifically determining the disinvestment of a not profitable or obsolete technology with a new replacing one, which will bring further benefits.

Questions arisen from the analysis of literature mainly regarded the limitations of current models implemented by international experiences, the design itself of these models and the consequent

utility of both their components and results, the timeliness of decision making and, in the end, the proper definition of roles in the organizational structure of HTA. The opportunity to take part to the Lombardy Region VTS-HTA process was a practical ground on which further investigating issues unsolved, as it represents a remarkable Italian example, and best answering the first research question. In fact, in Italy a proper national agency which is deputed to the leadership of HTA evaluations and to the systematization of the related activities is still lacking, however a first role has been assumed by the National Agency for Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali – Age.Na.S.), which promoted the collaboration and coordination for the systematic assessment of healthcare technologies at regional level (Rete Italiana di HTA – RIHTA) and the activities of Horizon Scanning (HS), which detect the possible impacts of emergent technologies on the SSN (Servizio Sanitario Nazionale – National Health Service). Thus, the Lombardy Region became aware that a proper development towards sustainable effectiveness and appropriate decision making in the current economic situation couldn't be successful without the consolidation of *legitimized* practices for assessing both healthcare programs and technologies, the *leverage* on distributed *individual knowledge* that belongs to professionals – physicians, engineers, economists, lawyers, etc. – who contribute with their daily practice to both the delivery of care or the advancement of knowledge in healthcare, and the constitution of formal *benchmarking activities* with leading international and national agencies. The VTS-HTA framework, which adapts elements from the EUnetHTA and the EVIDEM frameworks, standardized three elements, i.e. the *model*, the *actors* and the *process*. First, the *model* is the knowledge base adopted for the multidimensional and evidence-based assessment. It examines eight dimensions of evaluation for healthcare technologies, as easily comparable to domains of the EUnetHTA Core Model; explicit tools for the appraisal of evidence were adopted from the EVIDEM model, which thoroughly takes into consideration strengths and weaknesses of the technology itself. The VTS model counts on 21 criteria, of which 15 are defined as computable, since they are referred to properties which can be measured; the other remaining 6 criteria are considered intrinsic because it is questionable to refer them to specific measurable properties and their evaluation is strictly connected to an overall judgment of the specific context. As the overall process is subdivided into the three stages defined by NICE, different functions of phases correspond to different roles of *actors* involved. First, the General Healthcare Directorate is charged of planning and technically controlling the health policies under evaluation. A technical contribution to the General Healthcare Directorate is also provided by a group of professionals who operate in two evaluation bodies, the Unit of Prioritization and Conflict of Interests (Nucleo di Valutazione Priorità e Conflitti di Interesse – NVP-CI) and the Regional Technical Roundtable for Medical Appropriateness (Tavolo Tecnico Regionale per l'Appropriatezza in Medicina

– TTRAM). The first group is responsible for the first phase of prioritization of technologies to be evaluated, while the second one accounts for the final appraisal of technologies themselves. Besides these permanent bodies, the General Healthcare Directorate is assisted in its decisions by an Assessment Workgroup (Gruppo di Lavoro – GdL) of qualified experts, who are chosen on the purpose of a definite evaluation as specific witnesses of a scientific domain coming from different backgrounds, professional organizations and scientific schools. Thereafter, the different phases of the VTS *process* consist in (a) acquiring and prioritizing requests of healthcare technology assessment (Prioritization), (b) performing a multidimensional and evidence-based assessment of the technologies themselves (Assessment), and (c) appraise the results (Appraisal). Each step produces a specific output which will be input for the following phase: in fact, the Prioritization will define whether a technology deserves interest or not, with the editing of a related Rapid Report and the application of the MCDA model by weighting and scoring dimensions; when proceeding to the Assessment phase, a structured multi-criteria report will be produced, namely SIM (Stima di Impatto Multidimensionale – Multidimensional Impact Estimate). This document collects evidence from literature, with additions provided by experts, and is stratified according to the different criteria of the MCDA model; this will be then input for the final judgment of the Appraisal jury, which will evaluate each described criterion by allocating weights, representing their relative importance to the decision maker, and scores, which assess the performance of each option against criteria, in order to calculate the MCDA Index in the form of a weighted sum. After analyzing results and opinions of each member, the process ends with the final decision of appropriateness of use for the technology under evaluation, a public consultation and a formal Regional act.

After a first presentation of the workflow of activities, the involvement in a specific technology evaluation was established to focus on the peculiar model which is used for priority setting and to determine its level of current efficiency. In fact, the previous activity resulted to be functional, in this perspective, to better understand how documentations are structured and elaborated to support effective decision making and how actors are involved to efficiently combine their knowledge for process advancement. The case of the procedure for Patent Foramen Ovale (PFO) closure, an intervention to repair a heart defect which is aimed at treating recurrent stroke and migraine, was presented and followed from its early Prioritization stage to the Assessment, which is the point currently achieved. More specifically, the policy question in Lombardy Region was presented during a meeting regarding another technology, when some cardiologists reported the issue of PFO closure, as an intervention which caused significant complications in some cases, requiring re-hospitalization expenditures and creating discomforts for patients. Against an arguable effectiveness of the procedure, the General Healthcare Directorate thus decided to deepen this point of question and

undertook a rapid literature search on Google Scholar and CADTH (Canadian Agency for Drug and Technologies in Health) HTA reports, which gave the first hints on PFO closure cases. After the request provided in November 2011, an independent Rapid Report (RR) was completed, shedding light on the technology under consideration, on comparators and main expected impacts on the system. Anticipatory weighting and then scoring of dimensions, with the addition of comments, were afterwards implemented by the NVP-CI members, in order to perform the “Multi-Dimension” Decision Analysis and synthesize the Priority Judgment. Furthermore, the General Healthcare Directorate identified the typologies of domain experts needed for the following phase, which were formally requested to hospitals, Local Health Authorities, and foundations, to Medicine and Pharmacy university faculties, as well as to NVP-CI and TTRAM members themselves, and confirmed upon verification of secondary interest by the NVP-CI.

The Assessment experts defined the boundaries of the evaluation and the objectives of the SIM redaction, i.e. the identification of criteria for appropriateness of use (and a possible registry of patients’ clinical pathway through the treatment of this disease), the identification of qualified centers for the implementation of the procedure, and the revision of the reimbursement tariff. At this point, tasks were subdivided among different experts, and Coordinators for the evaluation were appointed in order to determine process owners who could encourage direct participation of members. A collaboration was started with Age.Na.S., the National Agency for Regional Health Services, to develop a rapid HTA with a systematic review of literature, moreover the analysis of the regional Data Warehouse was commissioned by the General Healthcare Directorate in order to corroborate literature results with contextual information. More specifically, this latter document confirmed a strong warning for inappropriateness and necessity of disinvestment of some centers which implement the procedure occasionally, however further in-depth examinations are needed about patients follow-ups, which are lacking up to now.

Separately from the VTS-HTA procedure, it was then decided to simulate the process of redacting the SIM, which is part of the Assessment phase, in order to better understand how the process in Lombardy Region actually works, and to focus on its inefficiencies and issues: the SIM reproduction started from the collection of documentation through a literature search, which was supervised and driven by a Coordinator of the PFO evaluation, and resulting articles were then clustered according to the disease and the typology of study; afterwards, sources were analyzed and information was separated in order to appropriately complete selected issues. During the study, this relevant step was valuable to directly face real problems which panelists meet in their task, thus a thorough reflection on purpose and meaning of each component enabled questions to be solved in order to improve the overall process.

The observation of the process was not an end in itself, since, instead, many argumentations arose from the necessity of making leaner and more effective the as-is complex system. In particular, the analysis of the VTS-HTA framework led to the third research question and to the subsequent contemplation of each single component characterizing two main pillars which were identified: on the one hand the decision making model, which was embraced by incorporating and contextualizing other international examples, and, on the other hand, the organizational structure, which both affects and is affected by how the process itself is designed. Further explanations of why problems had consistence and how they could find a way for solution were then followed by the formulation of recommendations for both the decision model's and the organizational structure's issues, which should induce an improvement on how the process is perceived by its main users. More specifically, this crucial point for the research reported the current "as-is" aspects and problems with the proposal of "should-be" options for change (where "R" are major and "r" minor recommendations), distinguished between MCDA (1) and organizational structure (2) issues as follows:

1.1 Scores – The twofold question regards the current low level of engagement of TTRAM members: is low participation due to the complexity of the process itself, to the necessity of creating an alignment of competences into the group, and to the lack of appropriate information? Why should they express different scores for a certain evaluation, instead of a univocal performance level?

R1.1 Scores, which represent the performance of the technology under evaluation related to the different criteria, should be first suggested by Assessment experts themselves, who express a "univocal utility function" that is directly connected to both their literature review and their knowhow, in order to provide a first orientation for TTRAM members and further engage them in a better understanding of the SIM.

1.2 The first two criteria, i.e. C1 – Completeness and consistency of documentation and C2 – Relevance and validity of documentation, are considered additive to other ones, while already affecting their evaluation. Is it right that evaluations with a higher grading of C1 and C2, but poorer in other criteria, have more advantages than those ones where happens the opposite?

R1.2 C1 and C2 should be separated from other criteria, since their evaluation is already implied when rating other criteria themselves.

1.3 Why issues are repeated in some SIM criteria, thus creating overlapping information?

r1.3 Overlapping issues should be eliminated in order to make the asking and answering process leaner and more understandable with both exhaustive and mutually exclusive information.

1.4 Weights - Why the weighting scale has limited 1-15 ranking, being adapted in order to avoid the association of the same mean weights?

r1.4 The weights could be freely associated to criteria with the allocation of 100 points.

1.5 Why weights of distinct groups of technologies should be maintained different?

R1.5 Weights should be maintained different in order to avoid bias which may occur if the specific context is not thoroughly taken into account.

2.1 Does an Assessment group composed of only clinical experts have the most appropriate capacities to provide an overall documentation about the technology of interest, to indicate possible lacks on methodologies, or to specify how to edit a HTA report?

R2.1 The panel of experts should include not only clinicians or health staff, but also properly selected patients' associations, health economists, and personnel with organizational competences, in order to take part to the elicitation of literature and to more effectively complete the SIM issues.

2.2 Does the TTRAM composition affect the usefulness of the MCDA Index? Should a proper balance of covered areas be reached in order to guarantee more reliability of results?

R2.2 The TTRAM group should be well-balanced according to different areas and understanding of the process, while the MCDA Index should be taken into account as a means of legitimizing appropriateness of use judgment.

2.3 Is the VTS-HTA program sustainable over large scale evolution of the activity?

R2.3 The VTS program will have to clearly define in which situations is needed to develop a HTA report (HTA Doers), and when to endorse already available studies properly checked and validated (HTA Users). In order to make the process of technology evaluation faster, a structured protocol for the Assessment phase has to be detailed from the perspective of a future increase of requests.

Finally, this research highlights crucial points of consolidation towards which the current practice has to move, as this novel proposed approach is not based only on the necessity of a different mindset, but also on the creation and exploitation of enabling factors which emerge through the analysis of methodological tools and the proper engagement of actors. The in-depth understanding of causes and impacts of choices on the healthcare system should instill a even higher sense of responsibility in both experts and final decision makers about what is being implemented. Moreover, the constructive comparison and rethinking on models of other international organizations, Lombardy Region collaborates with, results to be useful in a long term attitude of engagement for appropriate, robust and responsible choices.

Sommario

La sempre maggiore attenzione alla corretta allocazione di scarse risorse economiche, e la necessità di gestire un mercato di nuove tecnologie sanitarie sempre più in crescita, implicano la ricerca delle soluzioni più efficaci e utili; questo è ancora più evidente in un contesto nazionale di *spending review*, dove recenti normative hanno imposto meccanismi di generalizzata revisione e razionalizzazione della spesa pubblica nel tentativo di evitare la riduzione del livello di servizio. Di conseguenza, l'Health Technology Assessment (HTA) è emerso come uno strumento importante per sostenere le funzioni principali di un sistema sanitario efficace, in quanto le sue quattro caratteristiche principali sono (Cicchetti, 2008):

- orientamento delle politiche sanitarie,
- contenuto e processo interdisciplinari,
- utilizzo di diverse metodologie di analisi, compresi i metodi per la sintesi dei risultati,
- enfasi sulla disseminazione e comunicazione dei risultati ottenuti.

Alla luce di questi elementi di base, una buona gestione può contare sull'HTA per fornire un approccio di policy che è responsabile per le decisioni nei confronti della popolazione, e per questo motivo le organizzazioni specializzate nella valutazione delle tecnologie sanitarie stanno diventando elementi istituzionali dei sistemi sanitari, non solo per aiutare a identificare interventi sanitari che possono non essere efficaci, ma anche per individuare le tecnologie promettenti che possono stimolare l'innovazione (WHO, 2011). In Italia, ad esempio, l'approccio per la gestione dell'innovazione tecnologica in sanità non è ancora molto diffuso e ben istituzionalizzato nell'ambito del Servizio Sanitario Nazionale (SSN); tuttavia di recente l'HTA è stato apprezzato anche a livello istituzionale come aiuto utile per favorire l'introduzione di innovazioni adeguate e per incoraggiare fortemente un atteggiamento culturale verso l'appropriatezza degli interventi.

A seguito di queste considerazioni, i confini della presente ricerca sono stati definiti concentrandosi su un macro-obiettivo, che si riferisce alla necessità di istituzionalizzare correttamente il processo VTS-HTA (Valutazione delle Tecnologie Sanitarie – Health Technology Assessment) di Regione Lombardia su larga scala, come il primo esempio strutturato italiano che rende possibile un decision making ben ragionato; perciò, questo obiettivo principale si declina nelle seguenti tre domande di ricerca (Research Questions):

- RQ1: L'attuale architettura del modello VTS-HTA è propriamente legittimata?
- RQ2: Il processo attuale è efficiente al fine di garantire un funzionamento diretto e trasparente dal punto di vista dello scambio di informazioni e della struttura organizzativa?

- RQ3: Quali sono le più importanti leve che guidano un miglioramento efficace sia della progettazione, che della struttura di gestione del processo?

Le risposte alle domande di ricerca sono state infine articolate come raccomandazioni proposte per il miglioramento del processo, le quali potrebbero essere presentate direttamente sia ai rappresentanti regionali del sistema VTS-HTA, sia ad altre organizzazioni internazionali che attualmente collaborano con loro.

A valle della revisione della letteratura che è stata eseguita per approfondire al meglio l'ambito di ricerca, l'HTA potrebbe essere definito come *"un campo multidisciplinare di analisi delle politiche. Esso studia le implicazioni dello sviluppo medico, sociale, etico ed economico, la diffusione e l'uso delle tecnologie sanitarie"* (International Network of Agencies for Health Technology Assessment, 2002). Pertanto, si comporta come un "ponte" tra chi sviluppa la conoscenza e chi fa scelte di investimento, grazie ad un approccio stratificato che supporta il processo decisionale a diversi livelli, come ad esempio a livello individuale o del paziente, al livello di assistente sanitario o istituzione, o al livello regionale, nazionale e internazionale. Dal momento che l'Health Technology Assessment considera una varietà di impatti tra cui l'efficacia, l'appropriatezza e il costo delle tecnologie, esso può essere intrapreso da diversi tipi di organizzazioni, appartenenti sia al settore privato, che a quello pubblico, e, a seconda dell'obiettivo della valutazione, diversi tipi di esperti sono necessari, come ad esempio (Goodman, 2004):

- Medici, infermieri, tecnici di radiologia e di laboratorio, e altri clinici e professionisti del settore sanitario;
- Gestori di ospedali, cliniche e altre istituzioni sanitarie;
- Manager biomedici e clinici;
- Pazienti e rappresentanti di pazienti;
- Economisti, avvocati, scienziati sociali, esperti di etica ed esperti in ambito decisionale.

In questo modo, da un lato l'Evidence Based Medicine (EBM), i.e. la Medicina Basata sulle Evidenze, e dall'altro le tecniche di valutazione vengono definiti come i pilastri della disciplina di HTA. Per quanto riguarda il primo concetto, diversi stakeholders sono coinvolti per determinare le attuali migliori evidenze dalla ricerca scientifica e medica, e quindi per applicare l'esperienza clinica e l'osservazione nel prendere decisioni riguardo alla salute dei singoli pazienti. Inoltre, diversi metodi sono stati elaborati per qualificare e valutare i livelli di evidenza forniti da tipologie diverse di studi, come la scala dell'Università di Oxford (Centre for Evidence Based Medicine – CEBM), o lo schema di ordinamento descritto dal "Grading of Recommendations Assessment, Development and Evaluation

(GRADE). Per quanto riguarda la struttura organizzativa dell'HTA, diversi modelli sono stati elaborati negli anni, con un grado maggiore o minore di integrazione e di creazione di una rete tra agenzie sanitarie, le quali stanno sempre più elaborando nuovi metodi per coinvolgere i punti di vista di pazienti e cittadini, oltre alle dimensioni clinica ed economica.

Il secondo concetto di base che si riferisce alla descrizione dei diversi modelli per le valutazioni economiche in HTA è importante in quanto il tema dell'allocazione delle risorse si è dimostrato rilevante nella maggior parte dei paesi industrializzati, in parallelo con il crescente bisogno di assistenza sanitaria espresso dalla popolazione. Di conseguenza, sono individuate tre categorie di costi da tenere in considerazione nelle analisi economiche: in primo luogo, i costi delle risorse consumate nel settore sanitario, in seguito i costi relativi alle risorse del paziente e dei suoi parenti, e, infine, i costi delle risorse di altri settori, ad esempio il volontariato, o aree correlate al contesto economico generale di un determinato paese. Pertanto, le metodologie più utilizzate per analizzare i costi sono tre: nell'analisi costo-beneficio (ACB), sia i costi, che le conseguenze delle alternative che vengono messe a confronto sono espressi in termini monetari; invece, nell'analisi costo-efficacia (ACE) la valutazione dei benefici si basa su unità di misura non monetarie, fornendo risultati in termini di "costo per unità di efficacia", che corrisponde al rapporto incrementale costo-efficacia dei programmi a confronto (RICE). Infine, l'analisi costo-utilità (ACU) misura l'espressione dei benefici e l'utilità acquisita dallo stato di salute, rappresentato in termini di QALY (Quality Adjusted Life Years), che è un indicatore che rappresenta la "speranza di vita ponderata" ottenuta grazie al programma/trattamento effettuato.

Questi prerequisiti sono stati significativi per una migliore comprensione dei fondamenti di base delle esperienze internazionali che hanno sviluppato diversi quadri di analisi in questi anni: il National Institute for Health and Clinical Excellence (NICE), che è stato istituito in Inghilterra e Galles, ha definito una procedura a tre livelli per l'HTA distinti nelle fasi di scoping, assessment e appraisal. Dall'altro lato, l'European Network for HTA (EUnetHTA) ha sviluppato sia un quadro strutturato, sia una rete di informazione per diffondere modelli decisionali sanitari e per supportare le decisioni di policy, vale a dire il Core Model di HTA. Inoltre, il Consorzio canadese EVIDEM (Evidence and Value: Impact on Decision Making) ha elaborato un framework volto ad aiutare l'HTA e un efficiente decision making sanitario con uno strumento che facilita la considerazione sistematica ed esplicita di molteplici fattori che possono influenzare le decisioni, l'Analisi Decisionale a Criteri Multipli (ADCM). Un'ulteriore indagine su questo metodo decisionale è stata intrapresa con una ricerca sul database SciVerse Scopus, in modo da evidenziare le sue caratteristiche dal punto di vista organizzativo: l'ADCM è un approccio metodologico che abbraccia differenti punti di vista relativi, attraverso la definizione di criteri pertinenti ed esaustivi, che caratterizzano le preferenze dei decisori; grazie

all'attribuzione di pesi e punteggi per ciascun criterio, la loro somma pesata identifica un Indice ADCM che può essere poi impiegato per definire la priorità finale delle tecnologie sanitarie. Un secondo metodo denominato Programme Budgeting and Marginal Analysis (PBMA) è stato descritto, in quanto sviluppato specificamente per determinare il disinvestimento di una tecnologia non redditizia o obsoleta con una nuova in sua sostituzione, che porterà ulteriori benefici.

Le domande emerse dall'analisi della letteratura hanno riguardato principalmente i limiti degli attuali modelli realizzati nell'ambito delle esperienze internazionali, la stessa progettazione di questi modelli e l'utilità conseguente dei loro componenti e dei risultati, la tempestività del processo decisionale e, infine, la definizione appropriata dei ruoli nella struttura organizzativa di HTA. La possibilità di prendere parte al processo di VTS-HTA in Regione Lombardia è stato un terreno concreto su cui verificare ulteriormente altre questioni irrisolte, in quanto esso rappresenta un esempio italiano degno di nota, e rispondere alla prima domanda di ricerca. Infatti, in Italia una vera e propria agenzia nazionale, che è deputata alla direzione delle valutazioni di HTA e alla sistematizzazione delle attività correlate, manca ancora, tuttavia un primo ruolo è stato assunto dall'Agenzia Nazionale per i Servizi Sanitari Regionali (Age.Na.S.), che ha promosso la collaborazione e il coordinamento per la valutazione sistematica delle tecnologie sanitarie a livello regionale (Rete Italiana di HTA - RIHTA) e le attività di Horizon Scanning (HS), che rilevano i possibili impatti delle tecnologie emergenti sul Servizio Sanitario Nazionale (SSN). Così, la Regione Lombardia ha compreso che un corretto sviluppo verso un'efficacia sostenibile e un appropriato decision making nell'attuale situazione economica non avrebbe potuto avere successo senza il consolidamento di *legittimate* pratiche di valutazione per classificare sia i programmi che le tecnologie sanitarie, la *leva sulla conoscenza individuale* distribuita che appartiene ai professionisti - medici, ingegneri, economisti, avvocati, ecc. – che contribuiscono con la loro pratica quotidiana sia alla prestazione delle cure, sia all'avanzamento delle conoscenze nel settore sanitario, la costituzione di *attività di benchmarking* formali con le principali agenzie internazionali e nazionali. Il framework di VTS-HTA, che adatta le configurazioni di EUnetHTA e di EVIDEM, ha reso standardizzati tre elementi, vale a dire il *modello*, gli *attori* e il *processo*. In primo luogo, il *modello* è la base di conoscenza adottata per la valutazione multidimensionale e basata sulle evidenze. Essa esamina otto dimensioni di valutazione per le tecnologie sanitarie, facilmente paragonabili ai domini del Core Model EUnetHTA; strumenti espliciti per la valutazione delle evidenze sono stati adottati dal modello EVIDEM, che considera in modo approfondito i punti di forza e di debolezza della tecnologia stessa. Il modello VTS conta 21 criteri, di cui 15 sono definiti come computabili, in quanto si riferiscono a proprietà che possono essere misurate; gli altri 6 criteri rimanenti sono considerati intrinseci (giudicabili), perché è discutibile riferirli a specifiche proprietà misurabili e la loro valutazione è strettamente collegata ad un giudizio complessivo del contesto

specifico. Poiché il processo completo è suddiviso nelle tre fasi definite dal NICE, le fasi presentano diverse funzioni che corrispondono a differenti ruoli di *attori* coinvolti. In primo luogo, la Direzione Generale Sanità si occupa della pianificazione e del controllo tecnico delle politiche sanitarie in corso di valutazione. Un contributo tecnico alla Direzione Generale Sanità è fornito anche da un gruppo di professionisti che operano in due corpi di valutazione, il Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse (NVP-CI) e il Tavolo Tecnico Regionale per l'Appropriatezza in Medicina (TTRAM). Il primo gruppo è responsabile per la prima fase di definizione della priorità delle tecnologie da valutare, mentre il secondo si occupa della valutazione finale delle tecnologie stesse. Oltre a questi organi permanenti, la Direzione Generale Sanità è coadiuvata nelle sue decisioni da parte di un Gruppo di Lavoro di Assessment (GdL) composto da esperti qualificati, che vengono scelti allo scopo di una determinata valutazione come testimoni specifici di dominio scientifico provenienti da background diversi, organizzazioni professionali e scuole scientifiche. Successivamente, le diverse fasi del *processo* di VTS consistono in (a) acquisire e dare priorità alle richieste di valutazione delle tecnologie sanitarie (Priorità), (b) eseguire una valutazione multidimensionale e basata sulle evidenze delle tecnologie stesse (Assessment), e (c) valutare i risultati (Appraisal). Ogni fase produce un output specifico che sarà input per la fase successiva: infatti, la fase di Priorità definirà se una tecnologia merita interesse o meno, con la redazione di un Rapporto Sintetico e l'applicazione del modello ADCM con la pesatura e l'associazione di punteggi alle dimensioni; quando si procede alla fase di Assessment, un rapporto strutturato a criteri multipli sarà generato, i.e. la Stima di Impatto Multidimensionale (SIM). Questo documento raccoglie le evidenze della letteratura, con integrazioni fornite dagli esperti, ed è stratificato in base ai diversi criteri del modello ADCM; questo sarà quindi input per il giudizio finale della giuria di Appraisal, che valuterà ciascun criterio descritto associando pesi, che rappresentano l'importanza relativa del criterio stesso secondo la prospettiva del decisore, e punteggi, i quali valutano le prestazioni di ciascuna opzione a seconda dei criteri, al fine di calcolare l'Indice ADCM sotto forma di una somma pesata. Dopo aver analizzato i risultati e le opinioni di ciascun membro, il processo si conclude con la decisione finale di appropriatezza d'uso per la tecnologia in corso di valutazione, una consultazione pubblica e un atto formale regionale.

Dopo una prima presentazione del workflow delle attività, è stato concordato il coinvolgimento nella valutazione specifica di una tecnologia al fine di concentrarsi in particolare sul modello che viene utilizzato per definire le priorità e di determinarne l'attuale livello di efficienza. Infatti, l'attività precedente è risultata essere funzionale, in questa prospettiva, a comprendere meglio sia come le documentazioni sono strutturate ed elaborate per supportare un processo decisionale efficace, sia come gli attori vengono coinvolti per unire in modo efficiente le loro conoscenze al fine di far progredire il processo. Il caso della procedura di chiusura del Forame Ovale Pervio (PFO), un

intervento per riparare un difetto cardiaco che ha lo scopo di curare la recidiva di ictus ed emicrania, è stato presentato e seguito dalla sua fase iniziale di Priorità all'Assessment, che è il punto a cui si è arrivati attualmente. Più specificatamente, in Regione Lombardia la Policy Question è stata presentata nel corso di una riunione riguardo ad un'altra tecnologia, quando alcuni cardiologi hanno segnalato il problema della chiusura del PFO, come un intervento che ha causato complicanze significative in alcuni pazienti, le quali hanno richiesto spese di ri-ospedalizzazione e hanno creato disagi ai pazienti. A fronte di una discutibile efficacia della procedura, la Direzione Generale Sanità ha quindi deciso di approfondire questa questione e ha intrapreso una rapida ricerca della letteratura su Google Scholar e tra i report di HTA del CADTH (Canadian Agency for Drug and Technologies in Health), che hanno fornito le prime informazioni sui casi di chiusura del PFO. Dopo la prima richiesta, che è stata presentata nel novembre 2011, un Rapporto Sintetico (RS) indipendente è stato completato, mettendo in luce la tecnologia in esame, i suoi comparatori e i principali impatti attesi sul sistema. La pesatura preventiva e quindi l'assegnazione dei punteggi alle dimensioni, con l'aggiunta di commenti, sono state poi attuate dai membri del NVP-CI, al fine di effettuare l'Analisi Decisionale a "Dimensioni Multiple" e sintetizzare il Giudizio di Priorità. Inoltre, la Direzione Generale Sanità ha individuato le tipologie di esperti di dominio necessari per la fase successiva, che sono stati formalmente richiesti a ospedali, ASL, e fondazioni, a facoltà universitarie di Medicina e Farmacia, nonché ai membri stessi di NVP-CI e TTRAM, e poi confermati previa verifica di interessi secondari da parte del NVP-CI.

Gli esperti della fase di Assessment hanno definito i confini della valutazione e gli obiettivi della redazione della SIM, vale a dire l'individuazione di criteri di appropriatezza d'uso (e un eventuale registro del percorso clinico dei pazienti attraverso il trattamento di questa malattia), l'individuazione di centri qualificati per l'attuazione della procedura, e la revisione della tariffa di rimborso. A questo punto, i compiti sono stati suddivisi tra i vari esperti, e sono stati nominati i Conduttori della valutazione al fine di determinare responsabili di processo che potessero incoraggiare la partecipazione diretta dei membri. Una collaborazione è stata avviata con Age.Na.S., l'Agenzia Nazionale per i Servizi Sanitari Regionali, al fine di sviluppare un "rapid HTA", con una revisione sistematica della letteratura, inoltre la Direzione Generale Sanità ha commissionato l'analisi del Data Warehouse regionale, al fine di avvalorare i risultati della letteratura con informazioni di contesto. In particolare, quest'ultimo documento ha confermato un forte monito riguardo all'inappropriatezza e alla necessità di disinvestimento per alcuni centri che attuano la procedura solo occasionalmente, tuttavia ulteriori approfondimenti sono necessari sui follow-up dei pazienti, che mancano fino ad ora. Separatamente dalla procedura di VTS-HTA, si è poi deciso di simulare il processo di redazione della SIM, che fa parte della fase di Assessment, al fine di comprendere meglio come il processo in Regione

Lombardia funziona realmente, e di concentrarsi sulle sue inefficienze e problemi: la riproduzione della SIM è partita dalla raccolta di documentazione attraverso una ricerca bibliografica, che è stata supervisionata e guidata da un Conduttore della valutazione del PFO, e gli articoli ottenuti sono stati poi raggruppati a seconda della malattia e della tipologia di studio; in seguito le fonti sono state analizzate e le informazioni sono state separate al fine di completare opportunamente gli specifici quesiti. Durante lo studio, questo passo importante è stato di valore per affrontare direttamente i problemi reali che gli esperti incontrano nel loro compito, quindi una riflessione approfondita su scopo e significato di ogni componente ha generato questioni da risolvere al fine di migliorare il processo globale.

L'osservazione del processo non è stata fine a se stessa, dal momento che, al contrario, molte argomentazioni sono emerse dalla necessità di rendere il più snello e più efficace l'as-is di un sistema che si presenta complesso. In particolare, l'analisi del framework VTS-HTA ha portato alla terza domanda di ricerca e alla conseguente riflessione su ogni singolo componente che caratterizza i due pilastri principali identificati: da un lato il modello decisionale, che è stato acquisito incorporando e contestualizzando altri esempi internazionali, e, dall'altro lato, la struttura organizzativa, che sia influenza, sia è influenzata da come il processo stesso è progettato. Ulteriori spiegazioni dei motivi per cui le problematiche hanno un determinato significato e come potrebbero trovare una soluzione sono stati poi seguiti dalla formulazione di raccomandazioni per le questioni riguardanti sia il modello decisionale, sia per la struttura organizzativa, che dovrebbero portare un miglioramento rispetto al modo in cui il processo viene percepito dai suoi diretti utenti. In particolare, questo punto cruciale per la ricerca ha riportato gli attuali aspetti e problematiche "as-is", con la proposta di opzioni "should-be" per il cambiamento (dove "R" sono raccomandazioni di maggior grado di urgenza e "r" di grado minore), che si distinguono tra questioni dell'ADCM (1) e della struttura organizzativa (2) come segue:

1.1 Punteggi – La duplice domanda riguarda l'attuale scarso livello di coinvolgimento dei membri del TTRAM: la partecipazione è bassa a causa della complessità del processo stesso, della necessità di creare un allineamento delle competenze all'interno del gruppo, e della mancanza di informazioni adeguate? Perché essi dovrebbero esprimere punteggi differenti per una determinata valutazione, invece di un livello di performance univoco?

R1.1 I punteggi, che rappresentano le performance della tecnologia valutata relative ai diversi criteri, dovrebbero essere in primo luogo suggeriti dagli esperti stessi della fase di Assessment, che esprimono una "univoca funzione di utilità" che è direttamente connessa sia alla loro revisione della

letteratura, che al loro know-how, al fine di fornire un primo orientamento per i membri del TTRAM e coinvolgerli ulteriormente in una migliore comprensione della SIM.

1.2 I primi due criteri, cioè C1 – Completezza e coerenza della documentazione e C2 – Rilevanza e validità della documentazione, sono considerati additivi agli altri, mentre ne influenzano già la valutazione. È giusto che le valutazioni con punteggio più alto di C1 e C2, ma più basso negli altri criteri, abbiano più vantaggi in termini di valutazione rispetto a quelli in cui avviene il contrario?

R1.2 C1 e C2 devono essere separati dagli altri criteri, in quanto la loro valutazione è già implicita quando gli altri criteri stessi vengono giudicati.

1.3 Perché i quesiti si ripetono in alcuni criteri SIM, creando in tal modo sovrapposizioni di informazioni?

r1.3 I quesiti che si sovrappongono devono essere eliminati al fine di rendere il processo di domanda e risposta più snello e più comprensibile, con informazioni sia esaustive, che mutuamente esclusive.

1.4 Pesi – Perché la scala dei pesi ha un ordinamento limitato da 1 a 15, per il fatto che è stato adattato al fine di evitare l'allocazione di uguali pesi medi?

r1.4 I pesi possono essere liberamente associati ai criteri con l'assegnazione di un totale di 100 punti.

1.5 Perché i pesi di diversi gruppi di tecnologie devono essere mantenuti distinti?

R1.5 I pesi dovrebbero essere mantenuti diversi per evitare distorsioni che possono verificarsi se il contesto specifico non viene preso in considerazione attentamente.

2.1 Il gruppo di Assessment composto da soli esperti clinici ha le capacità più appropriate per fornire una documentazione completa sulla tecnologia di interesse, per indicare eventuali carenze sulle metodologie, o per specificare in che cosa consiste la redazione di un report di HTA?

R2.1 Il gruppo di esperti dovrebbe includere non solo medici o personale sanitario, ma anche associazioni di pazienti correttamente selezionate, economisti sanitari, e personale con competenze organizzative, al fine di partecipare all'analisi della letteratura e di completare in modo più efficace i quesiti della SIM.

2.2 La composizione del TTRAM influenza l'utilità dell'Indice ADCM? Si dovrebbe raggiungere un corretto equilibrio di aree coperte al fine di garantire una maggiore affidabilità dei risultati?

R2.2 Il gruppo del TTRAM dovrebbe essere ben bilanciato in base alle diverse aree e alla comprensione del processo, mentre l'Indice ADCM dovrebbe essere considerato come un mezzo per legittimare il giudizio di appropriatezza d'uso.

2.3 Il programma di VTS-HTA è sostenibile in un'evoluzione su larga scala delle attività?

R2.3 Il programma VTS dovrà definire chiaramente in quali situazioni è necessario sviluppare un report di HTA (HTA Doers), e quando accorpare studi già disponibili, che vengono adeguatamente controllati e validati (HTA Users). Al fine di rendere il processo di valutazione della tecnologia più veloce, un protocollo strutturato per la fase di Assessment deve essere dettagliato in prospettiva di un futuro aumento delle richieste di valutazione.

In conclusione, questa ricerca mette in luce i punti cruciali di consolidamento verso i quali l'attuale pratica deve dirigersi, in quanto questo differente approccio proposto non si basa soltanto sulla necessità di un diverso atteggiamento mentale, ma anche sulla creazione e lo sfruttamento di fattori abilitanti che emergono attraverso l'analisi degli strumenti metodologici e il corretto coinvolgimento degli attori. L'approfondita comprensione di cause e impatti delle decisioni sul sistema sanitario dovrebbe instillare un senso di responsabilizzazione ancora più forte sia tra gli esperti, che tra i decisori finali, riguardo al valore di ciò che viene implementato. Inoltre, il confronto costruttivo e la riflessione sui modelli delle altre organizzazioni internazionali, con cui Regione Lombardia collabora, risultano essere utili in un approccio di lungo periodo, che è maggiormente coinvolto nel fare scelte appropriate, robuste e responsabili.

1. Introduction

1.1 Research Context

Healthcare technology is defined as the set of components which enables the supply of aid services, including not only all the instrumentation, equipment, drugs and medical/surgical procedures implemented in healthcare services, but also the organizational and staff systems thanks to which healthcare aid is provided. Consequently, Health Technology Assessment (HTA) has emerged as an important tool for supporting the core functions of an effective healthcare system, as its four main features are (Cicchetti, 2008):

- health policy orientation,
- interdisciplinary content and process,
- use of different methodologies of analysis, including methods for results' synthesis,
- emphasis on dissemination and communication of results achieved.

Given these basic components, HTA can be defined as the systematic evaluation of properties, effects, and/or impacts of healthcare technologies themselves; it is one of three complementary functions to ensure their appropriate introduction and use. The other two components are regulation, which is concerned with safety and efficacy, and assessment of all significant intended as well as unintended consequences of technology use; and management, which is concerned with the procurement and maintenance of the technology during its life-cycle. The performance of healthcare systems is strengthened when the linkages and exchange among these elements are clearly differentiated but mutually supportive. Thus, healthcare systems themselves can be strengthened when HTA is integrated into the human and material resources, data, transparent decision- and policy-making, and linked to the overall vision of equity and accountability.

Good governance can rely on HTA to provide a policy approach that is accountable for its decisions to the population, and for this reason organizations specializing in HTA are becoming institutionalized elements of healthcare systems, not only to help identify healthcare interventions that may not be effective, but also to identify promising technologies that can stimulate innovation (WHO, 2011). On the one hand, in fact, technology innovation enables conditions for growth through a networking exchange of information countrywide, by covering distances and improving communication between patients, doctors, facilities and institutions, so that experiences can be shared and information is instantly available when necessary on the internet. On the other hand, regarding the healthcare supply, it's important to point out that it is not an end to itself, but it is intended as an instrument at

the service of the relationship doctor-patient, with the priority to interpersonal relationships. Thus, HTA directly affects the decision making process, since it enables evidence-based health policy choices and prevents the supply of ineffective, inappropriate or unnecessary services, by controlling their related expenditures and improving the overall quality of medical assistance (Ricciardi, et al., 2010).

National contexts play an important role in patterning the overall conditions for evidence-informed policy. For example, the policy environment may vary from a closed and corrupted society to an open, accountable and transparent one. Political and social systems affect use of evidence itself in terms of timing and availability of resources, values, beliefs and ideology (Green, et al., 2007). Hence, if a “knowledge pull” from decision makers is present, the multidisciplinary and interdisciplinary nature of HTA shows the potential of providing information under a great variety of conditions. Introducing HTA into a health system can change the decision making dynamics over time (WHO, 2011).

In Italy, for instance, the approach for managing technology innovation in healthcare is not still widespread and well institutionalized in the National Health Service (in Italian, Servizio Sanitario Nazionale – SSN); however, recently HTA has been appreciated also at institutional level as a beneficial help for promoting the introduction of appropriate innovation in the healthcare system. An important opportunity was promoted and coordinated by Age.Na.S., the National Agency for Regional Health Services, which created the RIHTA (Rete Italiana HTA – Italian Network for HTA) as a means for interregional collaboration, in order to share experiences and results matured in different Italian organizations (Ricciardi, et al., 2010). The SSN is a “universalistic” system, which is addressed to the whole reference population without discrimination of gender, residence, age, income and job; thus, in recent years, besides the necessity of designing synergic healthcare networks, the ultimate methodological targets were the definition of basic needs and priority diseases, according to the analysis of epidemiological data, and, most importantly, the encouragement of a cultural attitude towards the appropriateness of interventions and the evaluation of their effectiveness through evidence-based medicine. Moreover, equity can’t be fulfilled without promoting appropriateness, which is intended as both clinical and efficient; in fact, a system subjected to overpressure of a not assessed and potentially inappropriate demand wouldn’t be able to guarantee equal supply of healthcare services to everyone, and, at the same time, resources wouldn’t be addressed to areas of major need (Ministero della Salute, 2006).

The healthcare expenditure, both at national and international level, is more and more growing compared to the development of single countries: regarding Italy, the Total Health Expenditure (THE)

reached a level of 10% on the total GDP (Gross Domestic Product) in 2010, being already at 7% in 1995 (WHO – Global Health Expenditure Database). More specifically, for instance in Lombardy healthcare represents the most relevant heading of the total regional expenditure (62,61% in terms of total committed expenditure), due to both the nature of services provided to citizens, and the amount of resources allocated for protection of the health of population. In May 2012, the urgent national regulations for *spending review* imposed mechanisms for revision and rationalization of the public spending, however organizations tried to avoid reduction of healthcare service level; areas which have been most affected by this procedure regarded the acquisition of goods and services, purchasing of drugs and biomedical equipment, consulting services and healthcare construction processes (Braghò, et al., 2012).

Broadening the perspective at international level, recent cost analyses point US as the country which leads the pack in medical inflation, as the cost of medical care has risen by 250% since the 1980s, and, for instance, the healthcare spending as a share of GDP is growing by around 1,4% a year. Other countries, as depicted and compared in the figure 1.1 below, present a high level of this indicator, exceeding the line 10% of the Gross Domestic Product, such as Canada, France and Germany. A recent theory stated by William Baumol argues that a “cost disease” caused by low productivity growth in healthcare affects costs, which will continue to rise in real terms, thus higher costs don’t depend on distortions, inefficiencies or market failures, but rather on something fundamental and unavoidable (Baumol, 2012).

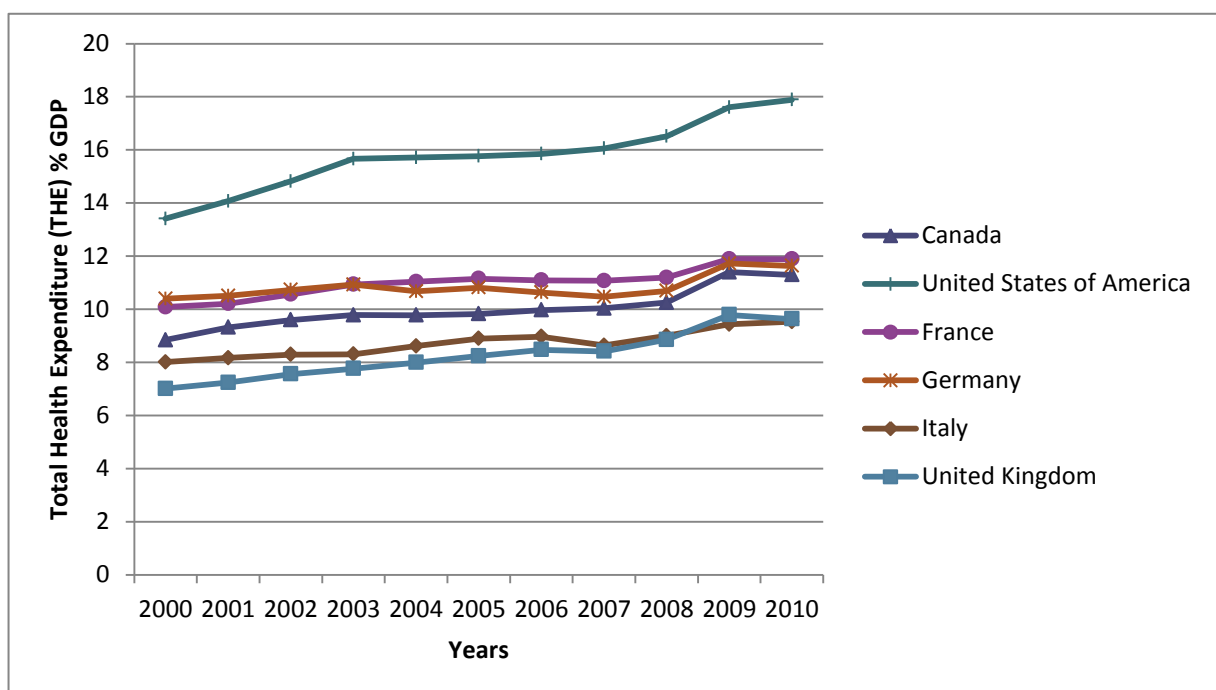


Figure 1.1 - Comparison of Total Health Expenditure (THE) as % of GDP in Canada, USA, France, Germany, Italy and UK

However, besides the conclusions of this theory, it's important to reach a sustainable system also in healthcare and its related innovation. Healthcare has many connected dimensions to be taken into account: technology, patient, organization and economics; among these, healthcare technologies have a predominant role in affecting the other components. Furthermore, correlated with the previous argumentations, there are four main perspectives against which the impacts of the adoption of a healthcare technology should be reviewed: increase of revenues, containment of costs, improvement of flexibility and creation of strategic options (Azzone, et al., 2002).

When dealing with HTA, the right decision making for technologies has to be implemented, starting from the request for evaluation: research questions determine how the rest of the assessment will be conducted, the aspects that will be evaluated and those that will not, thus their formulation is a crucial part of the assessment, since they transpose the original decision making problem, the policy question, into issues that can be answered by evaluating scientific evidence. Moreover, a broad integration of stakeholders' preferences in the decision making process, both internal ones, such as staff or patient groups, and external ones, such as institutional partners or government officials, is needed, in order to strengthen legitimacy and accuracy (Gibson, et al., 2004). From the economic side, HTA has the role of managing activities and also recommending for disinvestment in order to decrease costs as resources fail; methods for appropriate technology evaluation integrate principles of economic reasonableness, budget impact and comparative effectiveness evaluations, which reveal whether new interventions are superior to standard practice. More specifically, this latter practice is driven by the need to manage rising costs: in fact, health organizations strive to maximize healthcare services while living with balanced-budget requirements. For instance, US are one constituency now deploying comparative effectiveness research information because they need to balance their budgets and are under political pressure to both limit taxes and maximize services. This imperative focuses attention on the value received for the healthcare dollar spent. Thus, coverage decisions have a twofold influence: on the one hand, they can affect patient access to certain healthcare services, while, on the other hand, other incentives, such as board certification, can offer opportunities to educate and modify physicians' behavior (Holtz, 2007).

When assessing the dimension of appropriateness in healthcare, the basic steps to accomplish regard the search for appropriate information on expenditure and use of technologies, the statement of used methods, and the clarification of patients' needs. Decisions are made without perfect information, thus the best available knowledge has to be achieved by trying to involve physicians in the assessment process and to ask feedback from patients; this implies not letting limited information to limit decisions, and avoiding system fragmentation due to lack of information.

According to available evidence, HTA has to take into account the numerous factors at stake. Many international experiences developed different composite measures, such as the NICE (National Institute for Health and Clinical Excellence) in UK or the CADTH (Canadian Agency for Drug and Technologies in Health) in Canada, which uses methods that measure the relative importance and specific contribution of the technology value in the context of interest. Reasonableness in action is needed, furthermore it's important to finally make a decision, which entails coherent responsibility.

1.2 Goals of this Research

In this research context, it was important to focus on a peculiar example of HTA, i.e. the Lombardy Region VTS-HTA (Valutazione delle Tecnologie Sanitarie – Health Technology Assessment) framework, in order to determine reasons and methods for its effective and useful implementability. Furthermore, the system per se wouldn't be enough sustainable without the achievement of a robust level of agility against fast changes of both healthcare resources and needs for prioritization.

Thus, the macro objective driving this study is referred to the necessity of properly institutionalizing the VTS-HTA process at large scale, as the first structured example which enables well-reasoned decision making. Since the Italian National Health Service is so fragmented that providing unified guidelines is not possible, the starting point consists in making this system more ready, on the one hand, for standardization and international benchmarking, while, on the other hand, for responsible adaptability in order to face increases in requests for decisions. The renewal is even more crucial and of topical interest during this particular historical moment, as decisive choices are to be made in order to reorganize the composition of committees, which were elected in 2009 and ended their 3-year office in October 2012. The proposal of an improved system is, hence, functional to clearly prepare for a new regional deliberation which will take into account both strengths and drawbacks from the past, in order to finally set the VTS-HTA process as a relevant authority at national level.

Thereby, the concern of defining a decision making model which can fit current resources limitations and appropriate timeliness moved the following research questions, in which the macro objective is declined:

RQ1: Is the current architecture of the VTS-HTA model properly legitimized?

At this point, it will be important to clarify the main pillars on which this model is grounded, the dimensions to be taken into account for evaluation, and the actors involved. The connection between reliable Evidence Based Medicine and the achievement of a sustainable healthcare system has to be deployed, furthermore circumstances motivating for endorsement of certain decision making approaches have to be clearly sought.

RQ2: Is the current process efficient in order to guarantee a straightforward and transparent functioning from the perspectives of exchanges of information and organizational structure?

A thorough reasoning on the VTS-HTA framework will be facilitated by showing a pilot Assessment case study, i.e. the procedure for Patent Foramen Ovale (PFO) closure, which will be closely observed and simulated in some of its parts, with the aim of defining if and how the process actually achieves its final result, while better identifying features and inconsistencies which characterize the use of information generated and the organization of roles of different participants during each phase.

RQ3: What are the main levers driving an effective improvement of both design and management structure of the process?

The final goal will be, indeed, the consolidation of useful recommendations which will overcome current issues detected in the methodological tool, which is used for decision making, and the organizational configuration, in the attempt of reaching a consistent advancement of systematized judgments.

In this way, both the moment of transition for committees' renewal and the opportune critical attitude enable the exact timing for a new approach in order to overcome current practice, as a relevant added value to establish VTS-HTA as a robust broad-spectrum authority.

1.3 Organization of Contents

Chapter 1 includes a first introduction about Health Technology Assessment and general health aspects which characterize issues and criticalities of both the Italian and the international backgrounds. In light of this context, objectives of the study were specified in order to better focus on what for argumentations were posed and how contents were consequently organized.

In chapter 2, a thorough literature analysis is undertaken, by starting from the definition of the scope of literature review itself and then deploying available information about Health Technology Assessment, stratified according to its main components, i.e. the approach towards evidence and the organizational structure, with the addition of a peculiar section regarding current studies about patients' involvement. Furthermore, different typologies of economic evaluations are presented, in order to better introduce on which basis current international experiences ground their methods for priority setting of health interventions. In the end, specific methodologies are presented, of which one in particular, the Multi-Criteria Decision Analysis (MCDA), deserved attention thanks not only to its peculiar features and functionality, but also to its ongoing controversial use for legitimization of decision making; thus, it was chosen as the best area on which establishing further examination and remarks. Then, literature gaps were presented to highlight the necessity of new approaches.

Hence, chapter 3 describes the methodology which was performed in order to answer the emerged research questions and structure contents of the study, beginning from the involvement into a specific context, i.e. the Lombardy Region HTA system. Moreover, direct participation to different phases of the process enabled a in-depth reasoning on current practice, which led to the consolidation of recommendations for further enhancements that focused on specific components of the model itself and involved actors.

After a first overview on the Italian context and network, in chapter 4 features of the Lombardy VTS-HTA framework are described in detail, in order to answer to RQ1, by first clarifying roles of different participants and then distinct phases of the evaluation process itself: while incorporating and adapting components and structures taken from current international experiences, such as NICE (National Institute for Health and Clinical Excellence), EUnetHTA (European Network for HTA) and EVIDEM (Evidence and Value: Impact on Decision Making) Collaboration, the workflow of Prioritization, Assessment and Appraisal steps is clearly defined.

Then, to further focus on direct performed activities and to answer to RQ2, the opportunity of taking part to a specific technology evaluation is delineated in chapter 5, as the case study could be followed from its Policy Question to the Assessment phase, which is the point currently reached. Moreover, a simulation of the process of editing its most important document is implemented, in order to actually understand what are the main strengths and drawbacks on which panelists incur when completing a structured HTA report.

In the end, chapter 6 describes significant issues emerged from previous analyses, which could answer RQ3, by providing options for change and “should-be” recommendations in a view of future large scale development of the evaluation process itself: on the one hand, the MCDA tool has to be better understood, and, on the other hand, connected modifications of the organizational structure represent a further enabling step.

Thus, chapter 7 collects responses and reported conclusions about results obtained, with additional validation provided by final reflections with Coordinators of the evaluation; the last point regarded possible limitations of the research, as recommendations should be tested in practice while moving reflections at both Lombardy Region and international level.

2. Literature Analysis

2.1 Framing the Literature

The main purpose of this study is to describe how a decision model is used in the Health Technology Assessment context, and in particular how it could be legitimized thanks to both each component which characterize its design and the organization of stakeholders it involves. Furthermore, decision models are means and facilitators to the achievement of a certain outcome, since they constitute the main framework HTA agencies use at both global and local level, as it will be described further.

Thus, in order to best answer to the questions: how and why Health Technology Assessment rose among health organizations? Who is more involved in policy making at the international level? Which methods are implemented and are now pillars for decision making? the literature search is aimed at “collecting all the pieces” and tackling the following three main areas of interest:

- Legitimization of the HTA process, its approach towards evidence, its main actors, and definition of the economical evaluations which became bases and provided indicators for the decision making framework;
- Investigation of the international experiences developed over the years and their contextualization;
- Definition of the theoretic model, the Multi-Criteria Decision Analysis (MCDA), and its main features from the organizational point of view.

First of all, the increasing interest towards Health Technology Assessment completed year by year all the multidimensional streams which constitute this process: starting from the purpose of building evidence to be support decision makers in the most robust way, distribution of roles was defined, thus creating the first connections between institutions and their main users, patients. Thereafter, economic evaluations for health management were developed, in order to bridge both clinical and budget principles, namely analysis of social cost, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), and cost-benefit analysis (CBA).

Then, it was important to report how HTA is implemented around the world and who have been the first movers in creating *ad hoc* bodies, which now set the pace for standard procedures and institutionalize the HTA process itself. The main frameworks examined, and the respective evaluation methods are developed by:

- The National Institute for Health and Clinical Excellence (NICE);
- European Network for HTA (EUnetHTA);

- Evidence and Value: Impact on Decision Making (EVIDEM) Collaboration.

For each of these evidence corroborators, both an overview on the evaluation models and the contingencies which lead to the criteria on which they are based are deepened.

Third, a further search was undertaken to depict the decision model which is implemented at the moment in many international organizations: in fact, the MCDA is seen as the best “witness” which documents the multidimensional nature of healthcare decision making. More specifically, the literature search addressed the following issues:

- Description of the conceptual framework of MCDA in healthcare decision making;
- Identification of roles and interactions among the target group and the MCDA model itself;
- Definition of the main MCDA core values and its connection with the Programme Budgeting and Marginal Analysis (PBMA), another related priority setting framework.

Methods for the literature review will be explained at the beginning of each one of the next sections, thus defining clearly the rationale behind every step undertaken.

2.2 Health Technology Assessment (HTA)

As a prerequisite for a proper depiction of the background of the present work, pertinent articles and books were searched and analyzed in order to better understand the wide context of HTA, its main definitions, approaches and actors, who take part in the processes and structure its framework.

2.2.1 Introductory Elements and Key Features

At the origins, the term “Technology Assessment” was introduced in 1965 during deliberations of the US House of Representatives, where the Committee on Science and Astronautics was established with the purpose of providing information supporting policy decisions in the astronautic field, which was characterized by huge investments and extremely specific technical contents. Soon this Committee began to deal with health issues, when the Office of Technology Assessment (OTA) was founded in 1972, thus opening the door to a rapid research development in this field.

However, the first applications of Health Technology Assessment (HTA) started from a European country, France, where in 1982 the CEDIT (Comité d’Evaluation et de Diffusion des Innovations Technologiques) was established as the body which formulated recommendations for decisions regarding healthcare technologies and organizational innovation in the public hospital network of the city of Paris. Later, both in Europe and North America, many national and regional Agencies developed, until the INAHTA (International Network of Agencies for Health Technology Assessment)

was created in order to produce evidence to support policy making and to orient managers' and clinicians' decisions in health organizations (Cicchetti, 2008).

Thereby, HTA could be defined as *"a multidisciplinary field of policy analysis. It studies the medical, social, ethical and economic implications of development, diffusion, and use of health technology"* (International Network of Agencies for Health Technology Assessment, 2002). It behaves as a "bridge" between who develops knowledge and who makes investment choices, thanks to a multitier approach which supports decision making at different levels, such as individual or patient level, the level of healthcare provider or institution, or the regional, national and international levels. As a heterogeneous "modus operandi", the impetus for an HTA is not necessarily a technology, since HTA has three basic orientations:

- *Technology-oriented* assessments, which are intended to determine characteristics or impacts of particular technologies, such as clinical, economic, social, professional, or industrial;
- *Problem-oriented* assessments, which seek for solutions, strategies or practice guidelines for managing a particular problem for which alternative or complementary technologies might be used;
- *Project-oriented* assessments, which focus on a local placement or use of a technology in a particular institution, program, or other designated project, where facilities, personnel, or financial resources are important factors to take into account.

The Health Technology Assessment process investigates different domains of healthcare technologies, which, in general, include:

- Technical properties: for instance, performance characteristics and conformity to design specifications;
- Safety: it implies judgment of the acceptability of risk associated to the use of a technology;
- Efficacy and/or effectiveness: both refer to how well the technology itself improves patient health, by measuring certain health outcomes or endpoints. In particular, the former one refers to the benefit received under "ideal" or "controlled" conditions, e.g. within a protocol of a Randomized Controlled Trial¹, while the latter one refers to the benefit of using a technology for a particular problem under general or real conditions, e.g. in observational studies;

¹ A **Randomized Controlled Trial (RCT)** is a clinical study type which evaluates the consequences of a program with narrowly defined criteria, implemented on a chosen group of patients.

- Economic attributes or impacts: they are both from microeconomic and macroeconomic background, including on the one hand costs, prices, charges associated to individual technologies, and on the other hand national health care costs, resource allocation among different health programs or among health and other sectors, effects of intellectual property policies, regulation, third-party payment, and policy changes on technological innovation, investment and employment;
- Social, legal, ethical and/or political impacts: they arise in HTA in the form of normative concepts, such as valuation of human life, applications of technology in different phases of prevention, screening, diagnosis, therapy, research and upgrading of knowledge, integrity of HTA processes themselves. Although methods of translating these implications into policy remain relatively underdeveloped, great efforts are made to better identify and take into account these perspectives in order to develop a robust evaluation process.

As Health Technology Assessment considers a variety of impacts including the effectiveness, appropriateness and cost of technologies, it can be undertaken by different types of organizations, belonging both to the private and the public sector, e.g. health professions organizations, group purchasing organizations, policy research organizations, hospitals and healthcare networks, patient and consumer organizations, biomedical research agencies, health product companies and venture capital groups and other investors. Depending on the scope of assessment, multiple types of experts are needed, such as (Goodman, 2004):

- Physicians, nurses, radiology and laboratory technicians and other clinicians and allied health professionals;
- Managers of hospitals, clinics and other healthcare institutions;
- Biomedical and clinical managers;
- Patients and patient affairs representatives;
- Economists, lawyers, social scientists, ethicists and decision scientists.

Consensus for health policy decisions, oriented towards a proper use of healthcare resources, emerges from a cyclic process which associates specific roles to:

- Medical science;
- Information synthesis systems;
- Health Technology Assessment;
- Clinical guidelines;
- Quality assessment and revision.

Furthermore, HTA can be applied for decision making at three different levels of the healthcare system:

- MACRO level (HTA National Agencies and Organizations): dealing with service design and organization, market introduction, reimbursement, regulation policies for technologies; for instance, the INAHTA was established in 1993 and has now grown to 52 member agencies from 29 countries including North and Latin America, Europe, Africa, Asia, Australia and New Zealand, in order to cooperate and share information from different cultures;
- MESO level (Hospital based HTA): dealing with adoption, purchasing and monitoring of use of technologies for institutional management at local level;
- MICRO level (Clinical practice): supporting the elaboration of guidelines, diagnosis protocols, recommendations and quality test and assurance.

This three-tiered system enables the continuous upgrading of knowledge, which directly involves innovation: the “Triple Helix Model” by Etzkowitz (2000) shows that the possibility for scientific knowledge to become good innovation depends first on the capacity of *industry* to identify and fund ideas in their early stage; then, the support of *government* and *public institutions* through the creation of infrastructural and prescribed conditions necessary to promote the merger between *research* and industry represents the third blade. Innovation in the biomedical field is thus synthesized in three parallel processes:

- Innovation, combining intellectual, relational and economic capitals which generate new solutions, thanks to the complex interaction between different actors;
- Legislation, related to the eligibility for funding of innovative concept;
- Evaluation, which is put into practice by agencies which embrace HTA principles, provides information for policy makers, managers and health professionals regarding the introduction, use and dissemination of healthcare technologies, and covers social, economic and ethical factors.

At this point, it's clear that being advanced is not enough for technologies to be accepted, but they have to accomplish safety and bring a real benefit in terms of health and cost-effectiveness: HTA can be integrated into the triple helix as the helm which gives a direction to innovation processes, respecting patients' needs, sustainability requirements of healthcare systems and, most importantly, appropriateness of interventions (Cicchetti, 2008).

In addition to drugs, technologies that are most frequently assessed by institutions are medical devices, biomedical equipment, combined or emergent technologies, clinical procedures: according

to different national contexts, the HTA process can represent a means of providing just recommendations, or otherwise a real constraint for decision makers.

Besides the variation of scope, HTA activities involve the following basic steps (Goodman, 2004):

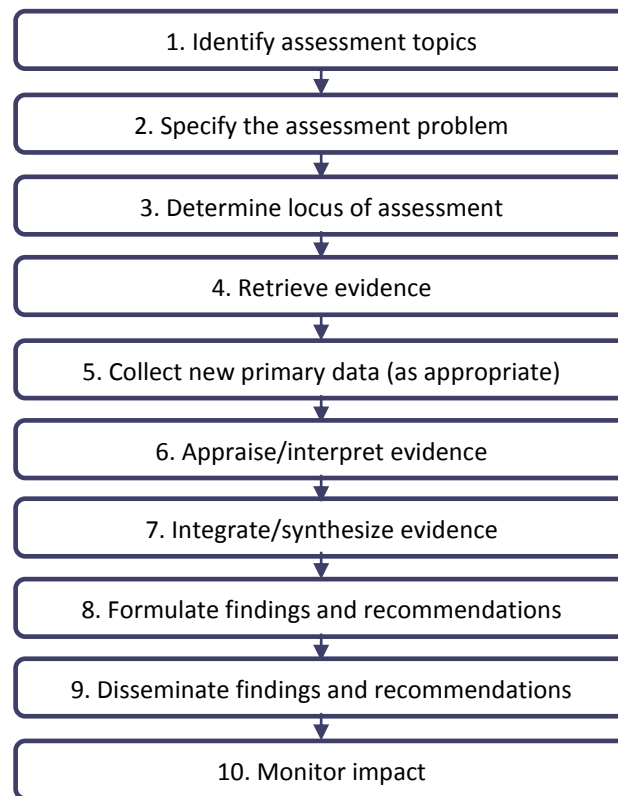


Figure 2.1 - Basic steps of HTA

The assessment rises from a evaluation request, and, after elaborating policy questions and collecting background information and current use of the technology, a first documentation of results is shared and discussed among stakeholders; subsequently, findings are disseminated and communicated to decision makers and are updated according to availability of resources and new competencies acquired.

2.2.2 Approach towards Evidence in HTA

By involving different stakeholders who give their contribution from many viewpoints, we can understand the concept of Evidence Based Medicine (EBM), which is a pillar of the HTA discipline, together with evaluation techniques (described further in the next paragraphs). EBM refers to the use of current best evidence from scientific and medical research, and the application of clinical experience and observation in making decisions about healthcare of individual patients. In this way, the single professional can merge his own knowledge and empirical experience to the information elaborated in other parts of the world, thanks to the fast development of IT solutions which make knowledge sharing mechanisms more transparent and interactive.

One of the essential requirements for the decision making process is, in fact, a proper understanding of the level of evidence associated to the sources of information and literature at each level of healthcare. Methods used by HTA for this purpose can be grouped into two broad categories:

- Primary data methods: involve collection of original data, ranging from more scientifically rigorous approaches such as randomized controlled trials to less rigorous ones such as observational studies and case studies;
- Integrative methods: also known as “secondary” or “synthesis” methods, involve combining data and information from existing sources, such as meta-analyses or systematic reviews to informal, unstructured literature reviews.

Primary data methods can be categorized in terms of multiple attributes or dimensions, for instance whether they are retrospective or prospective, interventional or observational, controlled or uncontrolled. Retrospective studies take into account past data, while prospective ones are implemented using real-time data, since events still have to happen when the study itself starts; this means that the process of collecting data is undertaken as patients are observed during the study, with more consequent time and resources consumption. On the other hand, the retrospective approach is less expensive, but some distortions can occur due to the difficulty of interviewees to remember (this is called *recall bias*), which causes misleading conclusions (Tarricone, 2004). In an interventional study, investigators prospectively deliver, manipulate, or manage the intervention of interest, while in an observational one investigators don't intervene, but rather monitor and follow an intervention. Many studies use separate control groups of patients as a basis of comparison to the one or more groups receiving a certain intervention, while some others do not use control groups, relying on comparing patient measures before and after an intervention to determine whether the intervention had an effect. Except for the intervention of interest, the treatment and management of control groups and intervention groups are as similar as possible, in order to compare incurring changes and isolate the effects of an intervention on patient outcomes from any other extraneous factors. Furthermore, assignment of patients to a certain intervention based on randomization is preferred to other means, such as alternate assignment or using birthdays or identification numbers, because it minimized opportunities for bias to affect the composition of these groups at baseline. Some studies employ blinding of patients, and sometimes of investigators and data analysts, of knowledge of patient assignment to intervention and control groups in an effort to eliminate the confounding effects of such knowledge (Goodman, 2004).

Randomized controlled trials (RCTs) belong to the category of experimental studies, which try to identify a cause-effect connection between the health improvement of patients and the fulfillment of

a certain program/intervention; specifically, they evaluate the consequences of the implemented program on the external environment and try to establish whether incurred changes among patients come from the intervention or they could happen also in its absence, thus being ascribed to environmental reasons. The main features of RCTs are the following:

- Patients are separated in treatment group and control group, as earlier described: just the first group is treated with a new program/technology, while the second one receives placebo or is treated with the comparison program. Patient allocation takes place randomly, i.e. with casual techniques.
- At the end of the time of the study, namely *follow-up*, outcomes of interest are measured and, by comparing the two groups, investigators can establish whether the new program is more effective or not with a well-defined statistical significance.

Clinical trials are considered to be the gold standard of epidemiological studies since, unlike other typologies of study (e.g. observational studies), they can control how much variables such as bias and confounding² can affect the outcome of interest. Thus, results from RCTs are “clean” from external variables influence and represent the impact of the program on the population of interest: the level of results precision depends also on sample size, follow-up duration and blinding of patients, investigators or both. The framework of a randomized clinical study is reported in the following figure 2.2.

² A **bias** is defined as any systematic error incurring when associating inaccurately risk factor and disease onset, or intervention and outcome of interest. **Confounding** errors occur when the association observed in the study is due not to the risk factor or the intervention, but to differences among the groups of enrolled patients.

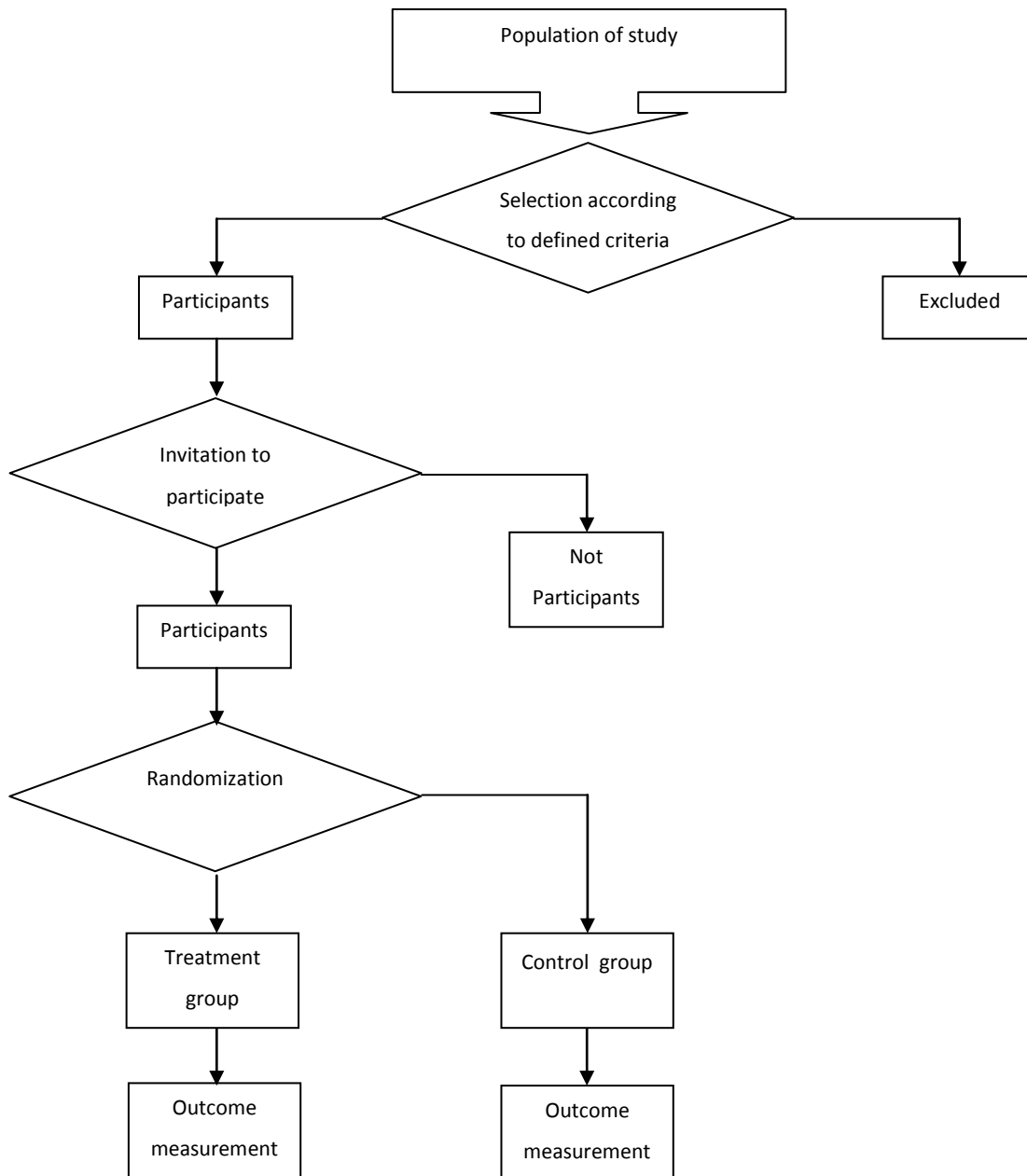


Figure 2.2 - Randomized controlled trial framework

Lastly, in order to define how to use studies of these typology to elicit effectiveness data, we have to assess whether it's more important quality of data, or their relevance. In fact, findings from clinical studies can be defined important for *efficacy*, obtained under controlled conditions, in contrast to *effectiveness*, obtained in actual conditions, which are relevant for public decision makers. From this follows that the selected sample for the clinical trial almost never represents the population of patients regularly treated in clinical practice, since inclusion and exclusion criteria of clinical studies usually select population with specific characteristics; thus, efficacy detected in clinical studies doesn't correspond to the one characterizing clinical practice, mostly when crucial factors for its extent are experience and/or skills of the clinician.

On the other hand, observational studies don't require modifications of current clinical practice, and the effect of the intervention is measured in actual and not controlled conditions. They include (Tarricone, 2004):

- Case-control studies (retrospective): patients are separated between cases, which receive the program of interest, and controls, which are treated with a different program, usually the current; the aim is verifying whether the impact of the new program on patients' health is significantly different from the control group one, but its limit is in how controls are chosen.
- Follow-up studies (prospective): once treated with a program (innovative vs current), patients are classified in two or more groups and followed for a certain time in order to identify and measure the outcomes of interest, so that a comparison is possible in the end. Still, losses during follow-up are significant, since patients lost during follow-up can belong to a particular category and invalidate consistency of results.

For many topics in HTA, finding the definitive primary study that settles whether a technology is better than another for a particular clinical situation is difficult, moreover different studies have to be combined and taken into account from a broader social and economic viewpoint in order to formulate policies.

Integrative methods include:

- Meta-analysis (typically used for topics without definitive studies, so that evidence collected for assessments often includes studies with insufficient statistical power (e.g. because of small sample size) to detect any true treatment effect. By combining results from multiple studies, this type of method may in the end have sufficient power to detect a true treatment effect);
- Modeling (e.g. decision trees, Markov models);
- Group judgment ("consensus development");
- Systematic literature review;
- Unstructured literature review;
- Expert opinion.

Most HTA programs use integrative approaches which distinguish findings according to stronger or weaker evidence drawn from primary data studies, which can be more or less available and rigorous. Since assessment orientations can vary due to the context where they are undertaken, resource constraints or other factors, evaluation programs tend to rely on different combinations of methods

which guarantee a certain level of validity. Programs belonging to the HTA process produce measures that can be easily interpreted and compared according to the original methodological design. Although these concepts are usually addressed to the first type of methods, they apply to integrative methods as well.

Internal validity refers to the extent to which a study represents the causal relationship between intervention and outcome of a certain investigation; for instance, this includes how much systematic or non-random errors in the data are minimized.

On the other hand, external validity refers to the extent to which the findings obtained from a study conducted under particular assumptions can be generalized to other circumstances; every time that the hypotheses of a certain study differ from the ones of interest, the external validity of findings is questioned (Goodman, 2004).

As the Centre for Evidence Based Medicine of the University of Oxford (CEBM) explains, in order to literally “find” the evidence for a certain recommendation, it’s important to follow these steps:

1. Identify terms to fit the PICO question (where PICO stands for Patient, Intervention, Comparison, Outcome);
2. Look for secondary sources (such as guidelines, evidence-based summaries, structured abstracts, and systematic reviews);
3. Search for primary sources about therapy, diagnosis, prognosis, aetiology.

To clearly highlight that clinicians must know that not all evidence has equal value, a framework has been developed in 1998 (last edited in 2009) to determine and classify the quality of evidence provided by research. In this first version, types of studies have been separated into categories (columns) designed to direct clinicians in answering clinically relevant questions. The levels of evidence range from 1 to 5, where Level 1 represents the highest quality and Level 5 the lowest: furthermore, Level 1 represents the most unbiased information available among the five types of clinical studies (well-designed RCTs), while Level 2 evidence is derived from nonrandomized cohort studies (which lack randomization and so represent a lower quality of study design). Level 3 evidence is derived from retrospective case-control studies and Level 4 represents data obtained from case-series studies or from poor-quality cohort studies or case-control studies. The lowest level of clinical evidence is obtained from anecdotal reports or expert opinion. Each level of evidence can be further subdivided into categories related to the assessment of the quality, quantity and consistency of the evidence itself, as it is depicted in the table below (see notes after the table).

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR – Systematic Review - (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies ³ ; CDR [†] validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR [†] with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies ³	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with > 80% follow-up; CDR [†] validated in a single population	Validating** cohort study with good+++ reference standards; or CDR [†] tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts++	All or none case-series	Absolute better-value or worse-value analyses +++++
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR [†] or validated on split-sample§§§ only	Exploratory** cohort study with good+++ reference standards; CDR [†] after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological	"Outcomes" Research		Ecological studies	Audit or outcomes research

³ **Cohort studies** are the analytic method of epidemiologic study in which identified subsets of a defined population are, have been, or in the future may be exposed or not, or exposed in different degrees to factors hypothesized to influence the probability of occurrence of a given disease or other outcome. The main feature is observation of large numbers over a long period (commonly years) with a comparison of incidence rates in groups that differ in exposure levels.

	studies				
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Table 2.1 - Levels of evidence from CEBM 2001

*	By homogeneity it's meant a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted below, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
‡	See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals. The Confidence Interval is the range around a study's result within which we would expect the true value to lie; it accounts for the sampling error between the study population and the wider population the study is supposed to represent.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.

§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.
§§§	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
††	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
†††	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
††††	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
**	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
***	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
****	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1 - 5 years chronic)

Table 2.2 - Notes

Along with levels of evidence, the CEBM has developed a systematic method for grading the recommendation to be used in clinical practice, regarding how well the evidence answers the clinical question of interest. The recommendation can be graded according to the quality, quantity, and consistency of available evidence, indicating how confident clinicians can be when making a clinical application of research findings, in particular:

- A: consistent level 1 studies;
- B: consistent level 2 or 3 studies or extrapolations from level 1 studies;
- C: level 4 studies or extrapolations from level 2 or 3 studies;
- D: level 5 evidence or troublingly inconsistent or inconclusive studies of any level.

“Extrapolations” are where data is used in a situation that has potentially clinically important differences than the original study situation. Furthermore, users can add a minus-sign “-” to denote the level at which that fails to provide a conclusive answer because:

- Either a single result with a wide Confidence Interval;
- Or a Systematic Review with troublesome heterogeneity.

Such evidence is inconclusive, and therefore can only generate Grade D recommendations (Phillips, et al., 2009).

The levels of evidence and grades of recommendation were developed in order to answer questions about the strength of evidence provided by a treatment and about whether to use the treatment itself. Although the levels are a useful tool, they showed not to be helpful in some cases, that’s why a new and more user friendly framework was developed in 2011. It is meant to be a heuristic that clinicians and patients can use to answer clinical questions quickly and without resorting to pre-appraised sources. Heuristics are rules of thumb that help making a decision in real environments, and often consist in as accurate as more complicate decision processes.

The process of revision of the CEBM Levels model was moved by these reasons:

- The Levels should be designed in order to be used as a search heuristic for busy clinicians and patients in real time in addition to serving as a hierarchy of evidence. It was necessary also to modify categories to represent the natural flow of a clinical encounter (diagnosis, prognosis, treatment, benefits, harms).
- All the relevant terms should be defined in an extensive glossary with definitions both technically accurate and easily understandable.
- Screening tests were sufficiently important to deserve a separate entry, and the importance of systematic reviews had to be emphasized.

In the new framework rows and columns are switched: each column represents a series of steps to follow when searching for likely best evidence (the strongest one is found furthest to the left of the Levels, while the weakest is to the right), and each row represents the types of questions the clinician is likely to face in the actual order he can encounter them. Questions about common and rare harms were added, while economic and decision analysis issues were omitted since authors think that further research, together with economists and policy makers, is required before pronouncing on what represents good evidence in these areas (Howick, et al., 2011).

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5*)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or “poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, or systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect	long-term harms the duration of follow-up must be sufficient.)**		
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

Table 2.3 - The new OECBM Levels Table

*	Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.
**	As always, a systematic review is generally better than an individual study.

Table 2.4 - Notes

Evidence for different outcomes may have different levels and can be obtained from different studies. While all outcomes may be covered in one study or review, it may be necessary to assess several studies with different designs, e.g. to find the benefits and harms of a treatment.

Another ranking scheme is called the Grading of Recommendations Assessment, Development and Evaluation (GRADE), whose working group began in 2000 as an informal collaboration of people with an interest in improving the present grading system in healthcare. Many international organizations have provided input into the development of the approach and more than 50 organizations worldwide endorse or use GRADE and its criteria to assess the quality of evidence and the strength of recommendations. Even though the quality of evidence might be considered as a continuum, this approach has four levels of the quality of evidence:

- High, which characterizes systematic reviews of randomized controlled trials: further research unlikely changes the confidence in the estimate of effect, since clinicians know the magnitude of the crucial benefits and risks;
- Moderate: further research likely has an important impact on confidence in the estimate of effect, and may change it;
- Low, such as from systematic reviews of observational studies: further research is very likely to have an important impact on confidence in the estimate of effect;
- Very low, where any estimate of effect is very uncertain.

Besides the study design, there are factors which can lower the quality of evidence, and factors which increase it, and everyone of them is subjected to judgment, as depicted in the table below:

Favorable factors vs Unfavorable factors	
Strong evidence of association	Serious or very serious limitation to study quality (design and execution)
Evidence of a dose response gradient	Important inconsistency of results
All plausible confounders would have reduced the effect	Some or major uncertainty about directness
	Imprecise or sparse data
	High probability of reporting bias

Table 2.5 - Factors affecting quality of evidence

Furthermore, the strength of recommendation, which is separated from the grading of quality of evidence, is defined in two levels, strong and weak (or conditional); determinants of this indicator are:

- Balance between desirable and undesirable effects;
- Quality of the evidence;
- Values and preferences;
- Costs (resource allocation).

More specifically, the approach grades specific recommendations related to alternative management strategies about patients, setting and interventions.

Although the advantages of including explicit definition and sequential judgments during the grading process, weighting the relative importance of outcomes, consideration of the balance between health benefits versus harms, burdens and costs, the main limitations of the GRADE system are due to its complexity and its applicability in other settings than clinical medicine (European Centre for Disease Prevention and Control, 2011). Due to this reason, the approach is continuously under development, in order to best fit to busy clinicians, who have only a few minutes to answer a clinical question and need a “fast and frugal” heuristic search tool to find and use the likely best evidence.

In order to assess in a proper way the evidence at the level of an individual study or a clinical study, content experts and evidence evaluation experts are assigned to programs and prepare background papers for the assessment group: notwithstanding the expertise required to thoroughly and accurately assess the evidence, even basic understanding of fundamental principles can help decision makers to appreciate the importance to health practice and policy of distinguishing between stronger and weaker evidence, or between different outcomes of alternative treatments. That’s why it’s important to explicitly link findings and recommendations to their respective quality of evidence, according to their inclusion and exclusion criteria, and their level of potential bias (Goodman, 2004).

2.2.3 Organizational Structure of HTA

Concerning who fulfils Health Technology Assessment, HTA agencies are the bodies in charge of dealing with decision making relationships at different levels, clinical, political (national and regional), and managerial, distinguishing themselves in many contexts in relation to setting, sources and extent of funding, typologies of evaluations, and knowledge creation and transfer about technologies. There are two typologies of agencies, the ones “dipped” into and linked to an explicit decision making process for price and reimbursement decisions, and the ones which operate “stand alone”. Although

at the beginning health organizations wanted to separate responsibilities regarding market regulations, bodies which produce scientific evidence and evaluations (HTA), and decision making, then many countries emphasized the importance of the bond existing between the impact of recommendations produced by HTA agencies and the actual impact of findings on the decision making system.

According to the organizational coordination of the HTA process and the numerous methods of collaboration in every country, there are four different models (Cicchetti, 2008):

- *Integrated model*: with a strong centralized direction, within which one or more agencies operate at national level and manage all (such as the Haute Autorité de Santé – HAS – in France) or just a part of the technology assessment process (such as the National Institute for Health and Clinical Excellence – NICE – and the NIHR (National Institute for Health Research) Coordinating Centre for HTA – NCCHTA – in England, and the Deutsches Institut für Medizinische Dokumentation und Information – DIMDI – and the Institut für Qualität Wirtschaftlichkeit im Gesundheitswesen – IQWiG – in Germany). In other countries such as Sweden and Denmark, evidence produced by agencies have high normative value for decision makers, and there's a formal and explicit link between the evaluation and the decisional moment anyways.
- *Almost integrated model*: one or more agencies operate at national level in order to produce evidence to support systemic decisions or provide and spread recommendations for clinical practice, without formal integration between evaluation and decisional moments (such as in Norway, Finland, Holland, Belgium).
- *Federal model*: it is widespread in national healthcare systems where there are defined autonomies for funding and managing healthcare services at regional (such as in Spain) or provincial (such as in Canada) level, with a resulting propagation of autonomous evaluation centers; however, there are interregional coordination configurations in order to better benchmark and share different “modi operandi” in defining studies requirements and in their management.
- *Network model*: the technology assessment system is structured as a central node with peripheral centers representing evaluation units which operate at hospital level or healthcare service organization; for instance, the DACEHTA (Danish Centre for Evaluation and Health Technology Assessment) in Denmark has gradually decentralized technology assessments by involving evaluation units in university hospitals, where the “mini-HTA” method is used and the recommendations produced are useful at national level. The

procedure consists in a flexible and dynamic tool which is adaptable to local conditions and can be integrated into budget and planning processes, so that current requirements for decision making are fulfilled. Where the problem or the application extends beyond a specific local context, however, this procedure can't replace a full-size HTA.

The information collected by healthcare organizations produce then different health technology assessment documentations, and specifically (Cicchetti, 2008):

- Assessment reports: full and exhaustive reports, coming from systematic reviews of the scientific evidence about a certain topics, with more focus on dimensions of efficacy, safety, appropriateness and effectiveness of healthcare technologies;
- Technical queries: brief reports resulting from rapid assessments which are aimed at providing a prompt and concise answer to who needs short term results;
- Fast response service: short reports answering very specific issues with a "help desk" approach;
- Horizon scanning (analysis of emerging technologies): publications highlighting technologies which are not employed yet or are not widespread in certain countries;
- Pre-assessment: evaluation process which is based on a limited or incomplete literature review;
- Investment budget for devices: it is based on principles and created with HTA tools, in order to define with an annual and long term perspective the internal allocation of technological resources;
- Clinical practice guidelines: analysis and synthesis as recommendations and scientific evidence for a certain technology or procedure.

Besides the multiple dimensions of these evaluations, the real aim for assessors is to provide and thoroughly document every rational step that leads to certain findings and conclusions for decision making. Countries all around the world differentiate their approach according to their specific context, but the main focus is always to merge properly the clinical background with the economic one, searching for a global alignment towards a common response to the problem of scarce resources, which is worsened by social and demographic phenomena, such as the progressively ageing population, the increasing demand for assistance, the new healthcare opportunities arising from the technical and technological development.

2.2.4 Patient Involvement in HTA

HTA multidisciplinary activities seek to determine intended and unintended consequences of using a healthcare technology, however most of them focus more on clinical and cost effectiveness rather than other dimensions, such as social and ethical aspects and patient perspective, thus overlooking important points of view that have to be taken into account. In scientific literature, there is a lack of documentation of patient or public involvement, maybe due to the fact that participation of patient is seen more as an end in itself, rather than a means, or as a bias source, and to the difficulty of evaluating their involvement without the support of widely accepted frameworks and tools. Some studies, usually more frequent in mental health field, report that focusing on the patient perspective raises important issues, so far ignored, related to the use of assessed technologies themselves.

On the one hand, the term “involvement of *public*” refers to both who provides societal or lay perspective about healthcare technologies and to who is directly affected by a given health condition or healthcare technology, and includes individual patients, service users, and the entities representing them (Gagnon, et al., 2009). On the other hand, the proper definition of “*patient*” refers to the current and potential health service user or beneficiary of a healthcare technology. Patients have valuable and personal experiential knowledge about a specific illness or condition, and can provide direct views about them. Furthermore, there are two reasons why patients should be included in HTA: the first reason is that, thanks to their cognition, they can enlighten and inform an HTA by describing benefits and disbenefits of treatments, explaining why some technologies that appear effective in clinical trials prove not to be so in real life; the second reason is concerned with improving transparency and openness in public policy, making more explicit the normative assumptions that support HTA recommendations (Facey, et al., 2010). Thus, there is general consensus on the need for more patient-centered HTA methods, since introducing these perspectives could allow more accurate assessment of the value of healthcare technologies.

In a recent review by (Gagnon, et al., 2011), in the conceptual model related to patient involvement, three main features arise: the domains of consumer involvement (the policy-making domain, the organizational domain, and the commissioning of research); the type of public (a societal or lay perspective: citizens and representatives of citizens; and the perspectives of those directly affected by a given health condition: patients, caregivers, and representatives); and the level of involvement (information, consultation, and participation). These three levels of involvement are defined as follows:

- *Information* is related to dissemination and communication of information to the public;

- *Consultation* includes different ways of gathering evidence by asking consumers about their values, perspectives, needs, or preferences to feed different phases of the HTA process (consumers are involved as human subjects or informants);
- *Participation* comprises collaboration of patients or the public in the HTA process, their engagement as partners in the HTA process, and at a higher level, their control over the HTA process itself, thus establishing a two way flow of information, unlike the first two levels.

Other dimensions are also explored, for instance the purpose and context of involvement, the type of healthcare technology evaluated, and the methods used to capture patients' or the public's perspective, as outlined in the figure below.

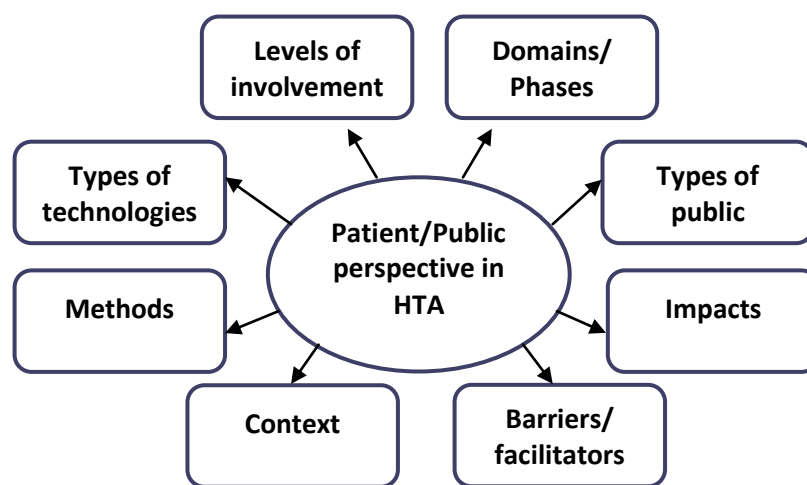


Figure 2.3 - Dimensions of patient and public involvement in HTA

A survey of the INAHTA showed that there is an increasing interest in involving patients and patient organizations in the deliberative processes of an HTA, but that their involvement is not widespread: in literature, the majority of studies which deal with this topic comes from United Kingdom, Canada, the Netherlands, Denmark, Germany, New Zealand and Austria, and tackles mainly the last two activities.

The purpose of *consultation* is mainly to explore perceptions, experiences or valuations of alternative technologies or substitute means of dispensing a certain service: qualitative methods such as interviews with patients or with people from support groups are the best strategies to provide health state evaluations, followed by focus groups; in addition to traditional methods, new emerging means are gathering information from social networks and weblogs.

In the second activity, public or patient representatives directly *participate* in three different stages of the HTA process, developing the assessment plan (or protocol, which allows patients' views and concerns to be considered in analyzing the issues), discussing the report and recommendations, and

disseminating results, such as UK, Canada and the Netherlands are already putting into practice. In this context, data are collected and different techniques can be implemented, such as deliberative dialogues, consensus conferences, nominal group techniques, Delphi methods, or citizens' juries. The quality of the deliberative process relies on participants' ability to contribute competently, and on the establishment of "fair deliberation" procedures. Patients' contribution to the HTA process and output is meaningful only thanks to early involvement, training about the process, technical language and topic under discussion, the choice of an appropriate participation method, and the impartial support of HTA organizations, which assume a role of moderators facilitating mutual respect and equal contribution.

Examples of involvement at the local level, such as in Quebec, Canada, regard also the activity of dissemination and communication of the HTA results: in this case, the focus group assumes a role of ambassador in "translating" the recommendations in the final report and making them accessible and useful to patients.

Moreover, the two elements most often associated with the usefulness of knowledge translation activities are the timeliness of data and the ongoing relationships between researchers and policy makers (Gagnon, et al., 2012).

To complete the analysis, barriers to direct participation of patients or the public in HTA activities entail the challenge of identifying and collaborating with appropriate consumers, which can be difficult, sensitive and time consuming issues, since groups who have very strongly held beliefs often could be less willing to be constrained by research evidence. Participation in evaluation activities requires some specific skills, such as the ability to work in a multidisciplinary team, and the unfamiliarity of both lay people and researchers to each others' needs and ways of working is another possible barrier. Furthermore, local initiatives are potentially more vulnerable to external pressures, thus research evidence could be compromised and biased. On the other hand, among facilitators of participation in HTA there are focused invitations (i.e. inviting people who have experience related to the topic), mentoring, training, and well-defined outcome-focused setting and timing of consultation activities provide an open working culture in HTA organizations which could facilitate public involvement.

Finally, even though further research is needed to explore this actual feasibility, these first studies show that the promotion of patient participation and of his sense of entitlement could improve the quality and safety of healthcare, thus plugging the gap between producers of HTA and its ultimate end-users, the patients.

2.3 Economic Evaluations in HTA

Evaluation models constitute the most important tools which connect theory with practice, thus a in-depth analysis of specific field and context books was undertaken, keeping in mind evolution and changes of contingencies throughout the economic system both at international and national level.

2.3.1 Resource Allocation and Costs Definitions

During the last years, the theme of resource allocation turned out to be dominant in almost all industrialized countries, in parallel with the increasing healthcare needs expressed by the population, which are determined, as earlier stated, by the progressive ageing, by the consequent growth of the rate of technology development and diffusion, and by the higher level of knowledge patients have about scientific information, thanks to its greater accessibility. If, on the one hand, patients become more and more conscious about available diagnosis and disease treatment solutions, on the other hand clinicians feel their increasing pressure for introducing and providing specific healthcare services, and have to deal with strict budget constraints.

Thus, economic evaluations are aimed at providing objective and rational direction criteria, in order to give contribution to healthcare decision making, and identify, measure and evaluate costs and consequences of compared alternatives. As international organizations in different countries show, a standard framework for economic evaluations doesn't exist, since peculiar variables which affect the role of assessment, the major/minor difficulty of measuring findings, and the institutional context can change decision making activities. According to the point of view adopted within the evaluation and the program description, it's important to identify which specific costs and consequences are to be taken into account; there are three categories of costs:

- Costs of resources consumed in the healthcare sector: they are related to the program implementation, included the ones of side effects, and variable costs such as time used by health workers, provided equipment, and fixed or general costs such as electricity, heating, rent and investment costs;
- Costs of patient's and his relatives' resources: they include all the expenses they're charged for, besides the value of every source they employ during the different phases of the treatment, for instance the time that the sick person or his family members take away from working activities in order to have a treatment or undergo a healthcare program;
- Costs of other sectors' resources (less relevant): for example, the voluntary work sector, or areas related to the general economic context of a certain country.

After the identification of relevant costs and consequences, the well defined next steps are their measuring and evaluation with proper units of measurement: common costs will be allocated to services or programs, while consequences weighted according to desired outcomes and effects. Furthermore, present and future costs of the program are evaluated in relation to a baseline year (usually the current one) in order to obtain an estimate of the overall value of resources absorbed, and the time when endpoint show themselves has also to be taken into account. Different programs can present different time profiles, as future costs and benefits flows couldn't have the same repercussions as in the present. In fact, the value associated to time in good health can be expressed in many ways: individuals appreciate more a better state of health life, and time in good health can be spent as free time, or as working time, which creates income for the individual himself and wealth for the society. This leads to a *time preference*, since not just at individual level, but also collective, having money or resources now, rather than in the future, is preferred, as it's possible to benefit from them in the meanwhile and as the existence of interest rates shows (Drummond, et al., 2000).

2.3.2 Analysis of Social Cost

Analyses of social cost represented the first form of economic evaluation in healthcare, since the aim was to determine the “economical burden of disease” for the society as a whole (patients, National Health Service, facilities providing non healthcare services, economic situation) in terms of direct costs, loss of productivity and intangible costs. The rationale was comparative, in order to weight costs of new preventive programs, with avoided disease costs in response to prevention. Traditionally, these studies took into account entire disease categories, and the costs detection was prevalence based in a top-down approach: used in United States, the whole national healthcare expenditure was classified for assistance typology and then allocated in one of the sixteen – now nineteen plus three supplementary classifications – disease categories of the International Classification of Disease (ICD). The advantage of this approach is that the sum of costs for every disease equals exactly the total national expenditure, but the drawback is that in so doing the national healthcare expenditure can underestimate or overestimate the direct total costs. Furthermore, non healthcare-related costs (such as transport or informal assistance) are usually excluded, representing a source of error where some diseases consume relevant quantity of these resources. Lastly, this method allocates the expenditure related to primary diagnosis, denoting a further bias since hospital discharges often involve multiple diagnoses and some diseases worsen or provoke other ones.

This global approach has been partially abandoned, in order to better focus on specific diseases. The main goals regard primarily:

1. Calculating the economic burden of disease for society as a whole, by providing information on the quantity of absorbed scarce resources, together with epidemiological data about morbidity⁴ and mortality;
2. Identifying the most important cost elements and their incidence on total costs, in order to stimulate further expenditure reduction policies;
3. Identifying the diagnostic-therapeutic pathway of sick patients at national level, in order to analyze and cut inefficient functions which can represent a first step for process reengineering;
4. Deepening the cost variability issue, by undertaking statistical analyses to check which information is more relevant for hospital managers and whether factors affecting variability are related to disease (e.g. gravity), patient (e.g. demographic features) or treatment facility (university or district hospital).

As previously stated, there are different features which can be evaluated in a social cost analysis:

- Healthcare direct costs: all costs carried by the National Health Service, by third parties (such as private assurances), by patients and their families to plan and make the program work, and they are connected to the whole healthcare resources consumption for prevention, diagnosis, therapy and rehabilitation (for example, hospitalization, outpatient treatment, home-care, specialist checkup, medical analyses, drugs);
- Non healthcare direct costs: all costs patients and their relatives, or others outside the healthcare organization are charged for, such as those ones related to transports to get to the program and to informal assistance provided by who's attending the patient.

In general, resources consumed as health services have to be evaluated in order to represent the opportunity cost of the benefits given up when employing resources for the chosen program. Furthermore, costs not supported in the future due to a new program have to be deducted from direct costs. Two main approaches were developed in line with economic accounting principles: the gross-costing approach (similar to top-down process accounting) splits up total costs of the supplying unit for the number of performances delivered in a certain period of time, thus calculating the average cost of healthcare service as the ratio of total costs of the unit and the number of performances undertaken; on the other hand, the micro-costing approach (similar to bottom-up product accounting) calculates the actual cost of services as the sum of all the "production factors" concurring to the service provision. The first approach is clearly less accurate than the second one,

⁴ **Morbidity** can be defined as the disease state or the degree at which the health condition affects the patient.

since it is not able to identify the extent of production factors consumption, but it's the less burdensome and faster than the micro-costing approach. The advantage of this last one is that it identifies the intensity of resources consumption by a specific patients' category, and differentiate it from other ones, thus the choice of which approach to use is connected to the relevance of the service on costs of the program of interest (Tarricone, 2004).

The primary methods of allocating indirect costs (such as administration expenses, central laundry, archive of medical records, cleaning service, electricity, etc) are, as economic principles show:

- Direct allocation: any general cost is directly allocated to final cost centers, according to how many hours a certain unit takes advantage of a service;
- Sequential allocation: all costs of business units which provide general services are sequentially allocated to the remaining units and final cost centers;
- Concurrent allocation: similarly to the previous method, all costs are allocated to all the business units which provide general services and to all the final cost centers, thanks to a system of equations which associate costs to every center according to services used by other cost centers;

Nowadays, the Activity Based Costing tries to identify the cause-effect relationship between the activities of both a intermediate and a final cost centers, by associating which activities drive and affect the final cost of a certain performance.

- Loss of productivity: the last category of costs is related to disability or early mortality due to the disease. This is basically measured according to the *human capital approach*, which assumes that the income received from working represents the production value of the individual: unfortunately, the approach was criticized for many reasons, as it discriminates workers from non-workers, people with higher or lower income, and it overestimates productivity losses because it considers in its calculations the whole absence time from working, by assuming full occupation in the society.

The productivity losses would be calculated in this way:

$$LPNW = PNW * (a) * (1 - u) * NAI$$

Where:

LPNW = loss of productivity from non workers

PNW = total number of non working patients (theoretical work force)

a = percentage to apply to PNW to estimate the active work force⁵

⁵ This data is available at national level from central statistics institutes (for instance, ISTAT in Italy).

u = national unemployment rate⁵

NAI = (total population) National Annual gross Income

Moreover, in order to overcome criticism, alternative approaches to human capital have been developed: one of these is the approach of *friction cost*, which hypothesizes that there is no full occupation and that productivity losses are referred to the time necessary to reset the production process, and not to the whole time during which the patient is absent from the working place. The friction time is thus defined as a time-window for adaptation, according to the availability in the market of skilled personnel and to the level of unemployment. However, even though this approach seems interesting for its theoretical basis, it's difficult to practically be implemented due to the necessary data, which are not always available at national level.

Lastly, social cost analyses can be classified according to these variables (Tarricone, 2004):

- Prevalence and incidence studies: they measure frequency of disease; prevalence studies measure the number of individuals who contracted the disease in a certain time and provide a probability estimate (risk) of getting sick.

$$P = \frac{\text{number of cases}}{\text{total population}} \text{ during a certain span of time}^6$$

Incidence, on the other hand, measures the number of new cases of disease spread among population at risk during a certain time span, providing a probability estimate that an individual at risk can be affected by the disease in a specific period of time;

$$I = \frac{\text{number of new cases in a defined time span}}{\text{total population at risk}}$$

- Prospective and retrospective studies: as thoroughly described in the previous section, they differ according to the temporal relationship between the beginning of the study and the data collection. In particular, retrospective studies are less expensive, but can cause wrong evaluations of costs, since people interviewed can report distorted memories about received treatments;
- Top-down and bottom-up studies: as previously described as cost evaluation methods, the first ones consider costs from a higher level, by allocating part of the healthcare expenditure to the disease or to an entire category of diseases, based on its/their prevalence. Bottom-up studies register punctual costs and quantity of employed resources, then aggregate every cost component on the single patient;

⁶ The indicator can be punctual or referred to a time lapse.

- Single-center and multicenter studies: regarding the number of facilities involved in the evaluation, which can affect how much findings can be generalized. Even though many studies can't be of the second typology due to time and budget constraints for research analyses, results from a single-center study can't be generalized at national level, but has just to give recommendations about the average cost per patient, clearly defining characteristics about patients and facility of study. Decision makers have to be careful about these data, since the national average resources consumption can't be represented and further studies are necessary to deepen the results.

Before the description of the most relevant methods for economic evaluations, it's important to highlight that every study has to follow a pre-defined protocol, where all the steps are described and documented carefully, in order to fulfill the best evidence requirements. More specifically about costs, a Canadian survey recently explained that healthcare resources evaluation in this typology of analyses usually takes into account:

- Average costs calculated throughout the study (for instance with gross costing and top-down methods);
- Tariffs: their use is proper just when the incidence of cost categories is not relevant, or when the perspective of the study is not the society as a whole, but a third party payer, such as the National Health Service or the single regions; in particular, normally tariffs aren't suitable for these analyses, since they represent prices, which are different from full costs of health services, and often depend on funding needs of the single facility;
- Monetary figures resulting from published available studies.

According to the perspective, on society in general rather than on comparative analyses, the trade-off still remains about building robust and evidence-based recommendations for decision makers on the one hand, and balancing scarce resources in a rational way on the other hand.

2.3.3 Cost-Effectiveness Analysis (CEA)

The effectiveness of a healthcare program is referred to its capacity of generating health, thus, when comparing two or more programs, it can be connected to a final outcome which is expressed in physical units of measurement of patients' survival, such as gained life-years or cases diagnosed, with the aim of maximizing benefits under budget constraints.

In the CEA the evaluation of benefits is based on non monetary units of measurement, providing results in terms of "cost per effectiveness unit", which is the incremental cost/effectiveness ratio of compared programs: since the maximization of health production is budget constrained, this means

that the last economic program implemented represents the cost/effectiveness ratio threshold. Hence, it's possible to determine the monetary upper limit beyond which the system doesn't allocate resources anymore.

The main phases for planning and implementing the CEA are the following (Tarricone, 2004):

1. **Programs identification:** during this phase it's important to choose the proper programs to compare, represented in the current clinical practice, supposing that they are the best option at patients' disposal.
2. **Effectiveness evaluation of each healthcare program:** as previously stated, in healthcare effectiveness of an intervention or a program is defined as the capacity of achieving positive results in terms of health for the community of patients. Thus, the features to clearly take into account during this phase are:
 - a. Effectiveness identification and measurement: at this point, the main impact on health of patients submitted to the program has to be measurable with a proper health indicator. If different programs provide the same effectiveness level, CEA becomes CMA (Cost Minimization Analysis), since, *ceteris paribus*, only costs of the programs have to be compared and the less expensive procedure has to be chosen. However, CEA can't consider different outcomes at the same time, thus one parameter is examined for effectiveness comparison with these solutions to the problem:
 - Another economic analysis can be chosen to evaluate the other various features of the program in monetary terms (health benefits, non health benefits, external benefits), such as the CBA, which will be later described;
 - Add the evaluation of secondary and non-effectiveness related effects to the calculation of costs;
 - Chose a clear and absolute effectiveness parameter which is both related to the main indication and reflects a positive improvement in health of the community, such as for gained life-years: measures of tolerability and program preference aren't part of effectiveness and can be evaluated with alternative techniques or included in costs calculations.
 - b. Relationship between intermediate and final outcomes: the first ones are relevant for the analysis only when there's a proven positive correlation between the intermediate and the final outcomes or when the intermediate outcome has a well-defined meaning connected to the survival of patients. For instance, the early

diagnosis of breast cancer has been demonstrated to be a predictive variable for survival.

- c. Effectiveness data sources and procedure of collection: the main source is the available medical literature, which is crucial for its quality and relevance; epidemiological studies are divided into experimental studies and observational studies, which have been previously described thoroughly; lacking epidemiological studies, experts' opinions can be examined in three ways:
 - Delphi method: the first step consists in selecting experts representative of the current clinical practice of the program of interest; they have to belong to different geographical contexts, different specialties and have experience acknowledged from the scientific community, while their participation is anonymous, in order to avoid that opinions of most influential people affect others'. Questionnaires are distributed to each expert in every round (at least 3-4), with increasing level of accuracy of required information, and the process continues in an interactive way until consensus is reached about the issues at discussion.
 - Modified Delphi method: it differs from the previous one for the number of rounds (here two at least), and the procedure of questionnaires distribution; for the first round it can be by mail (thus in anonymous form), and for the second round with a collective meeting, or directly with a collective meeting from the beginning. With this method experts' anonymity is not necessarily defined.
 - Experts panel: in a single round, the experts group provides information relevant for the economic analysis, thanks to a questionnaire, a paper collecting data, or a meeting. In this last case, experts can meet altogether or separately, then responses of each member are not shared among other group components.
3. **Cost evaluation of each program:** since effectiveness evaluation is referred to health measures (gained life-years), costs to be taken into account are only healthcare related, thus eliminating non healthcare costs and productivity losses. This last exclusion is aimed at avoiding discriminations of earned income between different contexts and countries: solutions can be defining a national gross income, which doesn't specify professional categories, or representing results separately from the monetary evaluation.

4. **Comparison of costs and effectiveness of programs:** once assessed costs and effectiveness of compared programs, the next step consists in calculating the Incremental Cost-Effectiveness Ratio (ICER). Indeed, a first screening of the situation has to be done in order to avoid unnecessary calculations; let's compare costs and effectiveness of two different programs A, the new one, and B, the one in use, as depicted in the figure below:

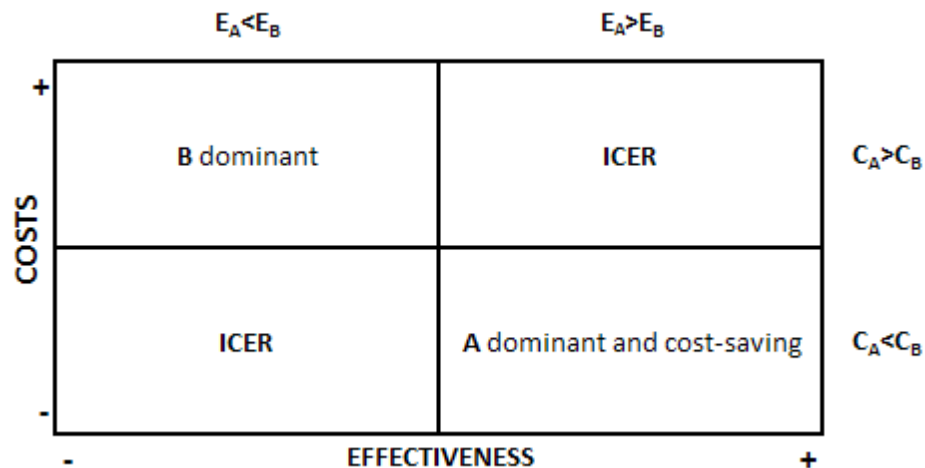


Figure 2.4 - Possible results of cost/effectiveness comparison of programs A and B

If costs of program A are greater than costs of B, and effectiveness of A is lower than effectiveness of B, then B is the dominant program and the new one has to be discarded; on the contrary, if costs of program A are lower than costs of B, and effectiveness of A is greater than effectiveness of B, then the program A is dominant and can be defined *cost-saving*, since frees resources that will be available for alternative purposes.

In the other two situations, it's necessary to calculate the Incremental Cost-Effectiveness Ratio as it follows:

$$ICER = \frac{C_A - C_B}{E_A - E_B}$$

More specifically, incremental costs, expressed in monetary units of measurement, are expressed by this formula:

$$\Delta C = \Delta C_d + \Delta C_{ae} + \Delta C_f + P - \Delta C_a$$

Where:

- C_d : direct costs of the treatment
- C_{ae} : costs due to adverse events, thus not expected
- C_f : costs due to future diseases, such as comorbidities incurred after the survival of the patient consequently the intervention
- P : productivity losses

- C_a : with negative mark, costs avoided in terms of healthcare and rehabilitation due to prevention or reduction of the burden of disease.

Improvement of clinical outcomes is obtained from the difference of programs' effectiveness, which are expressed by gained life-years in general terms (Y):

$$\Delta E = \Delta Y$$

At this point, the ICER has then to be compared with an acceptability threshold, defined from past investment plans, in order to decide whether the program is admissible for funding and check the financial availability afterwards. Once compared, the program can be declared feasible if a budget impact analysis confirms the financial sustainability.

Although this analysis is widespread both for clinicians' habit of evaluating healthcare programs according to their physical impact on population health, and for a cultural aspect, since the effect on health measured in terms of "gained life-years" is thought to be more appropriate for the healthcare sector, the CEA presents some limitations (Tarricone, 2004):

- Effectiveness of programs evaluated with different units of measurement (for instance gained life-years versus diagnosed cases) are not comparable;
- Different outcomes cannot be taken into account (such as mortality and morbidity);
- Giving different weights to different outcomes is not possible (i.e. survival has a greater value than adverse reactions).

2.3.4 Cost-Utility Analysis (CUA)

Pursuing the CEA path, the main feature of this analysis is adding to the expression of benefits the utility gained from the state of health, represented in terms of weighted life expectancy thanks to the program/treatment implemented. Since many diseases affect patients' lives not with mortality effects, but causing serious changes in their conditions, the aim of this analysis is measuring the individual quality of life and the possible positive or negative modifications following different healthcare procedures. More specifically, the features which determine the degree of integrity of the state of health are:

- Physical functionality
- Emotional functionality
- Sensory functionality
- Cognitive functionality
- Level of self-sufficiency

- Pain

This technique is aimed at making harm caused by the state of morbidity of the disease quantifiable, by detecting the relative importance individuals give to the loss suffered. Unlike the CEA, CUA outcomes can be single or multiple, since a synthesis indicator, the QALY (Quality Adjusted Life Years), is able to gather changes in both quality and quantity features of patients' lives and compare programs with a common unit of measurement.

There are two methods regarding how individuals perceive certain health outcomes, the first one measures directly preferences of patients, and the second one measures the state of health: measurement of preferences under certainty conditions detects values, for which Rating Scale and Time Trade Off approaches are applied; in risk/uncertainty conditions, utility is the only variable which can be identified, thanks to the Standard Gamble method. These techniques are briefly described below (Tarricone, 2004):

- In the **Rating Scale** method, the interviewee assigns a preference order to health outcomes and endpoints from the more favorite to the less one, by placing outcomes on a scale where spaces correspond to differences in perceived preferences. As depicted in figure 2.5 in the next page, the scale is a sort of thermometer which includes different categories and numbers from 1 to 10, or from 0 to 1, where the lowest value stands for the worst state of health and the highest value for the best one (usually perfectly healthy). The aim is eliciting the desirability degree of intermediate states of health as they are placed by the patient.



Figure 2.5 - Example of thermometric scale

- **Time Trade Off (TTO)** has been developed just for healthcare evaluations (Torrance *et al.*, 1972); here, two alternatives are presented to the person, who has to express the preference of interest:
 - Alternative 1: being in state A for a certain length of time t ;
 - Alternative 2: being in a state of perfect health for a time x , less than t , followed by death.

The outlined length of different states of health is changed until the interviewee declares himself indifferent regarding to the two alternatives: the indifference point expresses the value associated by the individual of being in a condition or another one, and determines the quality of life of state $A = \frac{x}{t}$. For an example, see figure 2.6 in the following page:

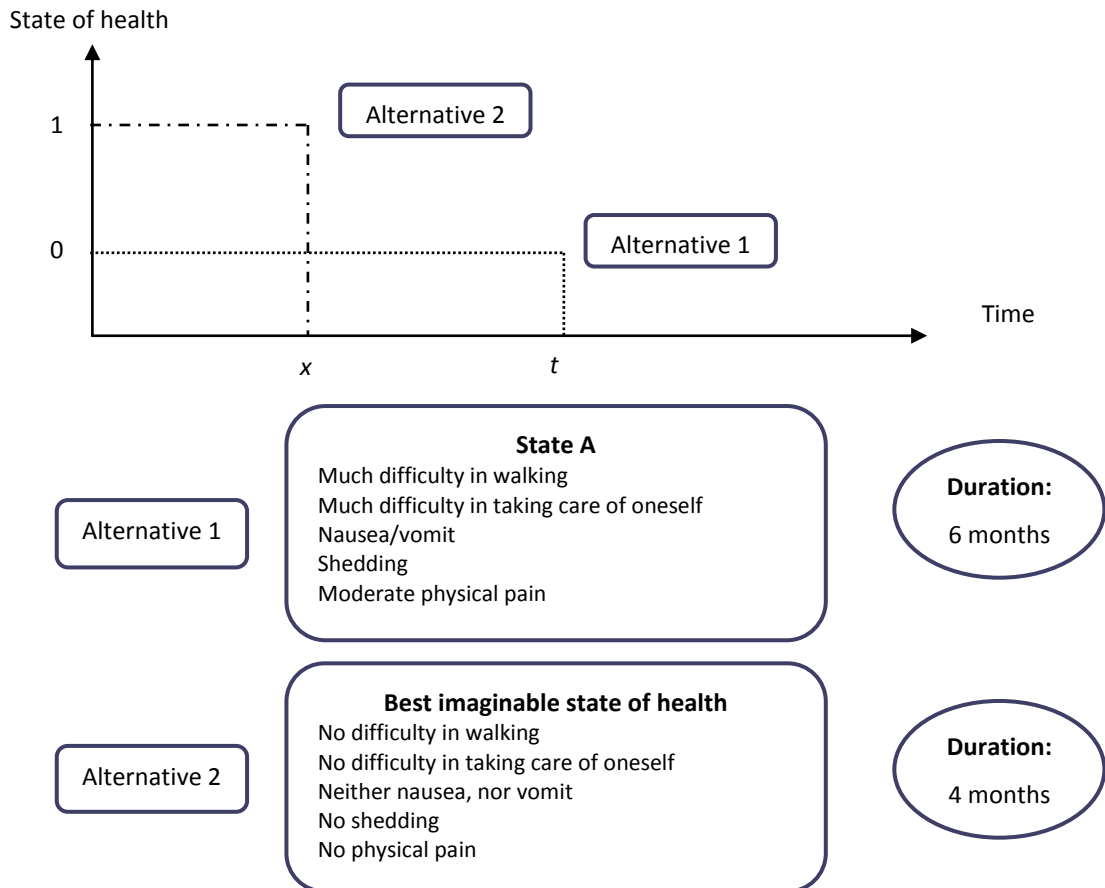


Figure 2.6 - Time Trade Off example

- The **Standard Gamble** differs from the previous method as the interviewee are offered two ideal alternatives, where to express his utility preferences:
 - Alternative 1: stay in a certain state of health A for indeterminate length of time;
 - Alternative 2: be treated with a hypothetical therapy which entails these inseparable effects:
 - a certain probability p of returning to a state of perfect health (for instance, 40% of probability);
 - a complementary probability $(1-p)$ of death (for instance 60% of probability).

The probability is changed until the patient declares himself indifferent to the presented alternatives, thus expressing the relative utility he associates in the hypothesis of being in a certain state of health. The higher is the risk he accepts in being in situation 2, the less desirable he considers his actual state (state A), insomuch as he is willing to a negative endpoint in order to try to reach a better health state. An example is represented in figure 2.7:

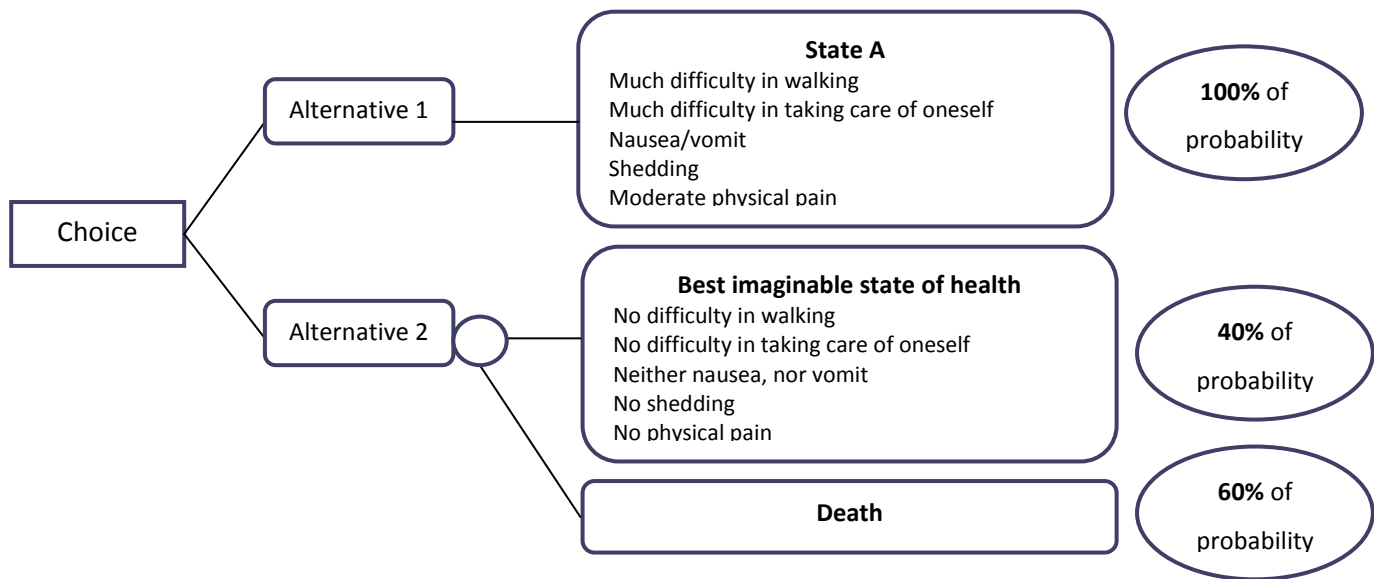


Figure 2.7 - An example of Standard Gamble

On the other hand, Health Related Quality of Life (HRQL) measures differ from preferences ones since they focus on the state of health and are aimed at clearly identifying the presence, absence, burden, frequency and length of specific symptoms or disabilities by making patients assign scores to different items taken into account. Unlike the expression of preferences, which provide an overall judgment on a certain state of health, here every single aspect is separately evaluated, by classifying measures with different typologies of scales: they are defined as “profiles” if the single determinants of quality of life complete a scoring system (disaggregate scales), while “indexes” if a global score sums up the overall dimensions (aggregate scales). More specifically:

- **Generic scales** are used to describe quality of life of patients with different pathologies among each other, both with dissimilar symptomatology and etiology, or individuals in good health; the drawback is connected to the loss of specific information regarding a given disease.
- **Specific scales** provide a less global view of quality of life by focusing on the physical or psychological profile of the person’s state of health.
- **Modified scales** are similar to the first ones, but include ad hoc dimensions of specific problems of the pathology of interest and the population under examination, thus covering both critical modification of the state of health and generic features of quality of life.

An example of generic measure of quality of life is the EuroQol (EQ-5D), which has been developed from a group of researchers (EuroQol Business Management Group) at the beginning of the Nineties. It is one of the more used scales, thanks for its brevity and easiness of implementation, as it considers five attributes: ability of movement, self-care, usual activities, pain or discomfort, anxiety and depression. Each attribute presents three levels: no problems, some problems, major problems,

thus defining a total of 243 ($3^5 = 243$) possible states of health combinations, to which “state of unconsciousness” and “death” have been added reaching a total of 245. A defined level of quality of life is associated to each state of health, which corresponds to a certain score on a 0-1 scale: every possible answer at each level for each dimension has a coefficient which measures the gap from the perfect state of health (score = 1) and the impact of the different dimensions on interviewed people’s quality of lives. Coefficients were determined thanks to a study applied to general people (more than 3000 people) in Great Britain using the Time Trade Off technique, and provide a five-digit number which describes the persons’ state of health, as it is illustrated in the questionnaire below.

Dimension/attribute	Coefficient
Constant	0,081
Ability of movement	
Level 1	0
Level 2	0,069
Level 3	0,314
Self-care	
Level 1	0
Level 2	0,104
Level 3	0,214
Usual activities	
Level 1	0
Level 2	0,036
Level 3	0,094
Pain or discomfort	
Level 1	0
Level 2	0,123
Level 3	0,386
Anxiety and depression	
Level 1	0
Level 2	0,071
Level 3	0,236

Figure 2.8 - EuroQol questionnaire and coefficients associated to the different levels

The score EQ-5D is obtained from the following equation:

$$EQ - 5D = 1 - \sum coefficients$$

For instance, the EuroQol of 11111 refers to an individual who doesn’t present any affection, while any other results below 1 represent the level of quality of life of patients in different situations. This tool is then helpful for the calculation of QALYs.

The QALY (Quality Adjusted Life Years) indicator summarizes in one number both the quantitative (reduction of mortality) and qualitative (reduction of morbidity) dimensions of life expectancy, which are weighted according to the relative desirability of different outcomes expressed by the individual:

in fact, it corresponds to the cost for each life year gained thanks to different options of a treatment. For instance, we can suppose that a patient affected by the pathology x is treated with a procedure which can increase of two years his expected life. Thanks to ex-ante and ex-post tests, the patient associates an improvement expressed with a score of + 0,5 points, compared to conditions before the treatment. From this follows that the resulting benefit for the patient is equal to 1 QALY (2 years x 0,5), which can be compared with the cost involved by the therapy. In other words, according to this patient, his perceived quality of life implies that two years lived in the actual condition equal one year passed in perfect health. As depicted in the next figure, the QALY calculation corresponds to the area below a certain state of health profile along time, multiplied for the perceived weight of quality of life according to different treatments.

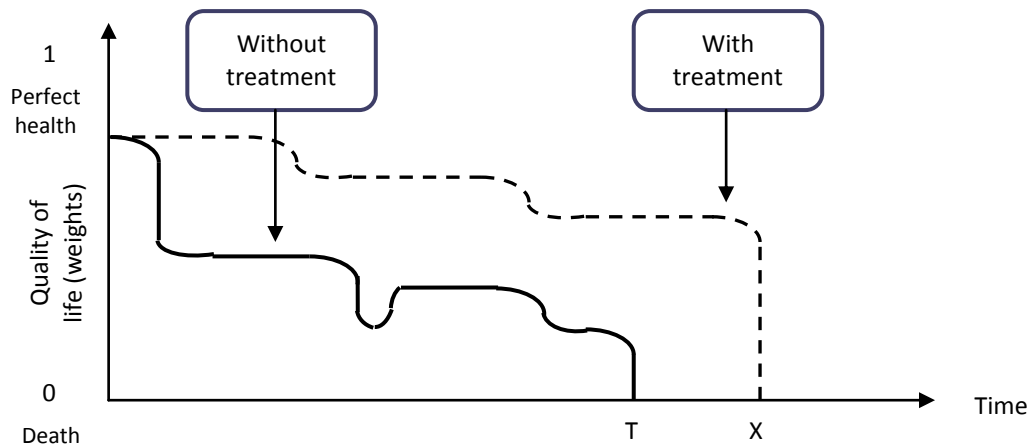


Figure 2.9 - Construction of QALY

The number of QALYs associated to each alternative is calculated in this way:

$$\text{Number of QALYs} = \sum q(t) \times t$$

Where:

- $q(t)$ = quality of life (utility) associated to a certain state of health
- t = length of time passed in a certain state of health.

If the program is not implemented, the life expectancy equals to the time T, and the quality of life decreases approaching to the point T (death); on the contrary, if the treatment is implemented, the individual can both live X years and have a better quality of life. Once calculated the number of QALYs, the difference between them represents the gained QALYs with the new therapy of interest. At this point, the result represents a term of comparison with the incremental cost of the treatment in object: a predetermined threshold defines its acceptability, while *league tables* provide decision makers with a list of programs ordered according to their cost-utility incremental ratio (Cost/QALY),

from the lowest to the highest one, and interventions are selected in descending order until available resources are exhausted. However, sometimes information provided in league tables is not sufficient to determine which individual intervention to choose and such problems often require the use of mathematical programming techniques. As any developed standard framework, these methods have to be properly adapted in order to be useful (Birch, et al., 2006).

2.3.5 Cost-Benefit Analysis (CBA)

In the cost-benefit analysis, both costs and consequences of compared alternatives are expressed in monetary terms, in order to provide a result as a cost-benefit ratio, or a simple difference between factors which represent the benefit/loss of a program compared to another one, and consequently the relative performance about estimated resources to use or save in each program. This analysis is typically used in situations where a public body with scarce resources has to choose between different competing programs which can't be implemented together at the same time. In this case, the two decisions to make are about affordability and then preference, to order priorities and classify programs. More specifically, the CBA compares the future flow of incremental benefits of a certain healthcare program, with the flow of incremental costs, so that the difference of these measures evaluates in the "social net benefit" of the intervention (see the formula below). If this result is positive (SNB>0), then the program is useful.

$$SNB = \sum_{t=0}^n \frac{b_i(t) - c_i(t)}{(1+r)^t}$$

Where:

SNB = social net benefit of the program

$b_i(t)$ = benefits (in monetary terms) related to year t

$c_i(t)$ = costs (in monetary terms) related to year t

r = discount rate for future flows

n = time horizon for the program

According to this approach, costs of the program are defined as "arising costs" (calculated as in the previous section), while benefits are identified as "avoided costs", which are classified according to:

- Saving of healthcare resources: quantified in number of hospitalization days, admissions, specialty performances, laboratory analyses, drugs, nursing care;
- Saving of productivity loss: interventions provided in day hospital or day surgery avoids staying in hospital for a long time, which enable savings for healthcare resources of the

hospital itself, for the patient and his relatives in terms of gained working time, and for the society as a whole in terms of earned production (or loss reduction).

In order to monetize healthcare outcomes, three approaches have been identified:

1. Human capital method: as explained in the first paragraph, use of healthcare programs can be seen as an investment in the human capital of an individual, thus stating that the time in good health of a person can be quantified as a productivity increase in the job market. Since the value of earned time in good state of health can't be monetized with the level of salary, which often is not pertinent due to inequalities for race or sex discriminations, two methods are presented (Drummond, et al., 2000) in order to link shadow-prices (defined for goods and resources not exchanged on the marketplace) with earned time:
 - Time opportunity-cost: the value of productivity has to be equal at least to the potential gain, thus time will be evaluated according to the lost salary;
 - Replacing cost: the calculation of how much the productivity of the individual could be replaced with services provided on the marketplace (hiring and firing costs).
2. Willingness to pay (WTP) method: it refers to how much consumers want to pay and to give up with other goods or services, in order to take advantage of benefits resulting from the program. In this specific context, benefits belong to these three categories:
 - Intangible health benefits: meaning health improvements thanks to the program, duration of the improvement, and probability of occurrence of the improvement itself;
 - Non-health benefits: related to value of the information, reduction of anxiety, and utility coming from the provision process of the healthcare program, such as behavior of healthcare personnel, place of the facility, waiting times, ongoing contact and rapidity of the analysis.
 - External benefits: related to the utility of knowing that access to the program is possible whenever is needed and to whoever asks for it.

Moreover, WTP can be measured thanks to the approach of expressed preference, i.e. by observing the real behavior of consumers, or with the approach of contingent evaluations, i.e. by assessing the possible behavior of consumers in an hypothetical marketplace, and quantifying not just future healthcare costs savings, but also the reduction of indirect costs and effects in the earned income. In fact, people interviewed are asked both the maximum willingness to pay for a healthcare program to be implemented (WTP), and the minimum compensation to refund a non implemented program (willingness to accept – WTA).

In conclusion, it's important to underline that the CBA is different from the simple comparison between arising and avoided costs: while these ones identify possible savings for the National Health Service thanks to a certain program, the complete CBA takes into account those procedures which maybe present avoided costs lower than arising costs, but positively welcomed by the community (Tarricone, 2004).

2.4 International Experiences

An appropriate view about the models developed by international agencies has been reached thanks to a search on their main official websites and through grey specific documentation available on the internet. Strengths and weaknesses of each experience will be illustrated, in order to better understand what are the current achievements and drawbacks each model has, thus adding both a practical description and a critical view.

In different international contexts, HTA agencies distinguish themselves according to the setting, such as the operational level they control in healthcare systems, the available sources for funding, the typology and depth of evaluations, their institutional responsibility and the relationships with decision making. For instance, regarding setting, there are two categories of agencies, the ones which work in behalf of communities of reference, usually national or regional, and the ones which operate directly in hospitals in order to support managerial and clinical decisions. Moreover, many agencies take advantage of public resources and are non-profit, but often they gain a relevant component of their funding from activities or services offered to industries (for example, the French HAS) or to insurance companies (for example, the German IQWiG). Most of the activities are related to healthcare technologies, while new fields of research involve the creation and diffusion of scientific knowledge, and its transfer among healthcare systems (Cicchetti, 2008).

2.4.1 Lessons from NICE (UK)

The National Health Service (NHS) was established to provide healthcare to all citizens according to their needs and not to their ability to pay. In order to face resources constraints and limited funding, since early 1990s evidence-based healthcare has become the main starting point to identify cost-effective policies and practices, and to give a role of reliability to scientific research decision making. The latest step came with the introduction in 1999 of the National Institute for Health and Clinical Excellence.

At the beginning, NICE was established in England and Wales, helping NHS in pursuing three objectives: improving the overall standards with continuity, reducing unacceptable variations in

clinical practice, and certifying the best use of resources to offer patients the greatest benefit (Walker, et al., 2007). Thus, NICE was established to produce guidance in four areas:

- public health – guidance for the promotion and protection of good health and the prevention of disease;
- healthcare technologies – guidance on the use of new and existing healthcare technologies (including drugs, medical devices, diagnostic techniques and surgical procedures;
- interventional procedures – guidance on the efficiency and safety of surgical, endoscopic and endovascular procedures and allied techniques;
- clinical practice – guidance on the appropriate treatment and care of people with specific diseases and conditions.

More specifically, regarding technology assessment, the key principles characterizing the NICE approach to decision making and guidance development are (Hill, et al., 2003):

- use of the best available evidence in decision making
- transparency
- consultation
- inclusion of all key stakeholders
- responsiveness to change.

An example of the guidance framework is provided in Annex A.

Appraisal processes are defined as single technology appraisal (STA) and multiple technology appraisal (MTA), while the three distinct phases of the last procedure, which is the most used, are:

- i. Scoping
- ii. Assessment
- iii. Appraisal

Scoping

The purpose of a scope is to provide a framework for the appraisal, by setting as thoroughly as possible the boundaries for the work undertaken by those producing reports for the Appraisal Committee, including the independent assessment groups and the manufacturers or sponsors of the technology (NICE, 2008).

During this process, both appropriateness of the remit and the specific questions to be addressed for each technology appraisal are determined, in order to clearly mark out the issues of interest, thanks

to the PICO (Population, Intervention, Comparison and Outcome) framework, for example (NICE, 2009):

- Population under study: Which populations are we most interested in? How can they best be described? Are there subgroups that need to be considered? Are there any relevant inequality or exclusion issues here?
- Intervention/approach: Which interventions/approaches/technologies should be used?
- Comparison: What is/are the main alternative(s), - including “usual practice” or “do nothing”?
- Outcome: What really matters to the population or individual? Which outcomes should be considered (for example, mortality, morbidity, relapse rates, physical and social functioning, costs, health status, and so on)?

Further issues for consideration include the costs to be addressed, the time horizon over which benefits and costs will be addressed, considerations of patients subgroups for whom the technology might potentially be particularly clinically and cost-effective, and issues relating to equalities legislation and/or the prevention of discrimination that may require special consideration.

Assessment

This phase comprises a systematic and independent evaluation of the evidence available on the technologies by an Assessment Group (an academic group commissioned by the NHS Health Technology Assessment Programme), in order to produce an estimate, taking into account of uncertainty, of a technology’s clinical and cost-effectiveness for a specific indication. Clinical effectiveness refers to the extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared to no treatment or other routine care, while cost-effectiveness refers to the value for money of a specific healthcare program, which provides a greater health gain than the one that could be achieved by using the resources in other ways (NICE, 2008). Evidence refers to quality, findings and implications of the technology, and has to discuss strengths, weaknesses and gaps of the contextual situation, in order to be relevant, complete, inclusive, and fit to purpose.

The assessment process always includes two mutually dependent components: (i) a systematic review⁷ of the clinical and economic evidence which includes submissions made by the technology

⁷ A **systematic review** aims at providing an exhaustive summary of literature relevant to a research question; for example, the Cochrane Collaboration, a group of 28000 specialists in healthcare who systematically review

manufacturers, and (ii) an economic evaluation which attempts to synthesize this evidence in the context of the NHS. More specifically, for MTAs, the Assessment Group conducts the whole first phase, while for STAs, the Evidence Review Group reviews the submission produced by the manufacturer or sponsor of the technology and provides a critique of this submission, sometimes recommending additional analyses or undertaking sensitivity analyses, such as exploring alternative scenarios and the uncertainty in the cost-effectiveness results.

- i) Systematic reviewing allows the efficient integration of evidence, so that it can be used for decision making: first of all, the primary research methods and designs used to measure the treatment effect are categorized into experimental studies (such as randomized controlled trials, RCTs) or observational studies, which present the lowest validity level. While RCTs have developed an important role in the clinical evaluations of healthcare interventions, their potential limitations for decisions concerning the efficient use of NHS resources are widely recognized. Factors such as partial comparisons (for instance, RCTs do not compare a treatment to all the comparators being considered by NICE) and short time horizon (for instance, they do not have a sufficient long period of follow-up to account for all treatment effects) often limit the value of RCTs as the sole basis of data for informing NICE guidance (Walker, et al., 2007). Therefore, good-quality non-randomized studies may be needed to supplement RCT data; in addition, the value of evidence from anywhere in the ranking will depend on its quality and relevance to the appraisal (as defined in the scope).

For its clinical guidelines, NICE has adopted GRADE methodology, as it has been previously described, in grading the quality of evidence, but it does not grade the strength of recommendations. Individual studies (for instance RCTs, cohort studies, case-control studies) are assessed using standard checklists to give a rating (++, +, -) that reflects the degree of confidence and the level of potential bias in the findings of the study. Information is collated in evidence tables and summary “evidence statements” that reflect the “strength of the

randomized trials of the effects of prevention, treatments and rehabilitation, as well as health systems interventions, outlines eight general steps for preparing a systematic review:

1. Defining the review question and developing criteria for including studies;
2. Searching for studies;
3. Selecting studies and collecting data;
4. Assessing risk of bias in included studies;
5. Analyzing data and undertaking meta-analyses;
6. Addressing reporting biases;
7. Presenting results and “summary of findings” tables;
8. Interpreting results and drawing conclusions.

Meta-analyses refer to methods which contrast and combine results from different studies, in order to identify patterns, sources of disagreement among study results, or other interesting relationships that may come to light in the context of multiple studies, starting from the identification of a common measure of effect size.

evidence” (number and types of studies, their quality and consistency of findings), the direction and size of effect (where applicable, for intervention and correlation studies) and its applicability.

While NICE doesn’t grade the strength of recommendations in its public health guidance, these take into account the “strength” of the evidence and its applicability, as well as the typical effect size (where relevant), the importance of the outcomes (including impact on inequalities), trade-offs between harms and benefits, cost-effectiveness and other issues such as equality and ethics (European Centre for Disease Prevention and Control, 2011).

- ii) The evidence requirements for economic evaluations include the quantification of the effect of compared technologies on the course of the disease of interest, the impact of those effects on patients’ HRQL and the evaluation of those impacts to reflect the preferences of the general population. The key features for economic evaluations involve different perspectives, which are connected to the previous section (Walker, et al., 2007):
 - a. Cost perspective: the costs to be considered relate to resources under control of the NHS and Personal Social Services (PSS), by quantifying the effects of interventions on their resources in terms of physical units (e.g. days in hospitals) and valuing those units in monetary terms using appropriate prices and unit costs. It’s interesting to notice that the Institute works in a specific context: some healthcare technologies may have a substantial impact on non-health outcomes or costs to other government bodies (for example, treatments to reduce illicit drug misuse may have the effect of reducing drug-related crime). Thus, these analyses will be presented separately from the appraisals;
 - b. Time horizon: since many technologies have impacts on costs and outcomes over a patient’s lifetime, such as it happens for chronic diseases, a long time horizon is required for any mortality component in order to quantify the implications of any differential survival effect between alternative technologies;
 - c. Cost-effectiveness analysis (CEA): this is the form of economic evaluation preferred, since both costs and consequences of an intervention are simultaneously considered against other relevant comparators. Merging it with the Cost-Utility Analysis, NICE specifies the QALY as its elected measure of health benefits and resource use which is under the control of NHS and PSS to measure costs for CEA, thanks to its synthesis of both mortality and HRQL effects. The EQ-5D is the preferred measure of HRQL in adults: as previously described, this system has been designed so that people can describe their own quality of life using a standardized descriptive system.

In order to assess whether the additional (incremental) costs of a new alternative are worth paying for the incremental benefits, QALYs are here used in order to calculate the ICER (Incremental Cost-Effectiveness Ratio) in this way:

$$ICER_{AB} = \frac{Costs_A - Costs_B}{QALYs_A - QALYs_B}$$

Where A and B represent two alternative treatments, and neither of them is dominant. At this point, the decision about whether an intervention is considered cost-effective hinges on the threshold ICER considered by the Institute to represent an efficient use of NHS resources. In principle, this threshold value should be determined by the displaced interventions, representing the health benefits forgone by implementing treatment A, for instance, but, when intervention to be displaced is not known, as decisions on this are made at local level, the approximated threshold is around £20.000-£30.000 per QALY.

Moreover, there are further appraisal considerations which deal with evidence, of both quantitative and qualitative origin, and specifically:

- Acceptability, appropriateness and preference: patients, carers, and healthcare professionals may prefer healthcare technologies because of the frequency or nature of adverse events or the route or frequency of administration, or, on the other hand, may be concerned about the ethics of using a particular technology. These are relevant considerations for an appraisal since they affect judgments on the usefulness of technologies, inform the nature of choice between alternatives and provide important evidence to adequately transfer in measurement of HRQL.
- Feasibility and impact: not just clinical and cost-effectiveness, but also organizational issues that impact on patients and carers, or those providing care, have to be taken into account to determine the rate of a technology's implementation and the size of its impact on the organization.
- Equity and equality: the first concept is intended in terms of how the effects of a healthcare technology deliver differential benefits across the population, which can be measured thanks to utility or societal values surveys, while the second one refers to the elimination of unlawful discriminations and the identifications, already from the scoping process, of groups who are relevant to the appraisal and reflect the diversity of the population (NICE, 2008).

Appraisal

This process involves the Appraisal Committee, which comprises a multidisciplinary group of independent experts including healthcare professionals, patient representatives and academics, and evaluates the outputs of the assessment phase within the context of additional information provided by consultees, commentators, clinical specialists, patient experts and general public. After considering the evidence, the AC formulates an appraisal decision based on a range of factors including cost-effectiveness, strength of the clinical evidence, robustness of the economic evaluation and the degree of clinical need of patients. The preliminary views on the technology of interest are summarized and detailed in the Appraisal Consultation Document (ACD), which is then widespread among formal stakeholders, such as patient/carer organizations, healthcare professional bodies and manufacturers, with an available month for comments. The final recommendations undergo a number of drafting stages with the Appraisal Committee before the Final Appraisal Determination (FAD) is agreed. The final review of the FAD and approval for distribution for appeal is the responsibility of the Institute's Guidance Executive: during this phase, the Appraisal Committee Chair is consulted to ensure that the Committee's deliberations are fully reflected in the FAD that is sent out for consultation. Subject to any appeal, the FAD will form the Institute's guidance on the use of the appraised technology. If any appeal is held and some or all of the appellants' points have been upheld, the Committee may need to meet again to review the appraisal: under these circumstances, the Committee may require further evidence from consultees, clinical specialists, patient experts and the independent assessment group.

Lastly, one of the main aims in establishing NICE was to facilitate quicker access to cost-effective treatments, however in 2005 the STA process was established as a tool to produce faster and rapid guidance for treatments, which would co-exist with the MTA process, observed to be "too slow". This was achieved by asking for a single submission of evidence by the manufacturer, which would be then independently assessed by an Assessment Group. On the other hand, a potential cause for concern of the STA process was both about whether the process itself will actually lead to faster acceptance decisions and about the shifting of the "onus of proof" to manufacturers, who clearly have an interest in seeing their product approved and in underestimating the ICER where a decision is on the margin, thus possibly undermining the independence of the NICE technology appraisal process. Anyways, published NICE appraisals are being used as international benchmarks, thus showing clear recognition of its credibility (Walker, et al., 2007).

On the contrary, it's important to note that during the last few years NICE has been strongly criticized not only for the slow release of its appraisals, which has delayed the availability of some treatments,

but also for its process of cost-effectiveness assessment, which is the most controversial aspect of NICE's work. Indeed, the analyses performed seem to be susceptible to biases, and the cost-effectiveness ratio may vary widely depending on assumptions made about clinical benefits and harmful effects or other factors. The cost-effectiveness ratio threshold has not been considered a rigid cut-off, furthermore there is no empirical research that tells us where these boundaries ought to be (Steinbrook, 2008).

First, the rationale of the CEA stems from the argumentation that by comparing the ICER, or price per additional QALY, of the intervention under consideration with an ICER threshold associated with their own subjective assessment, or in relation to the ICER of other interventions, decision makers concerned with maximizing health gain from available resources can determine whether the proposed intervention represents "value for money". However, although dividing incremental costs by incremental effects produces a price per QALY, this doesn't mean that any number of QALYs can be purchased at this price. On the contrary, this means that for an additional investment given by the incremental cost, additional health gains equal to the incremental effects could be produced. Thus, the ICER simply represents the average cost (or price) of these additional health gains, and can be used as a term of juxtaposition only when the interventions being compared have identical total costs (i.e. the alternatives are truly interchangeable).

Second, remarkably little attention has been given in the literature to how particular ICER thresholds are selected and, more importantly, how they relate to the opportunity cost considerations of the constrained maximization problem facing the decision maker. Communities with the same healthcare needs but different budgets will have different threshold values against which to judge the efficiency of interventions, furthermore information for healthcare decision makers is incomplete in the real world. Hence, lack of information prohibits determining the theoretically correct threshold or even a range within which it lies, resulting in the practice of determining arbitrarily and without any explanation of how application of a value limit leads to the efficient use of available resources.

In conclusion, the reputation about this cost-effectiveness indicator is even more controversial, as evidence from not only England, but also Ontario (Canada) and Australia shows that the application of the ICER approach to healthcare decision making have been associated with unplanned increased expenditures on healthcare interventions and concerns about the sustainability of public funding for those interventions without any evidence of increases in total health gains. For example, the estimated additional resources absorbed by NICE-recommended technologies in the first 2,5 years after the implementation of the NICE itself exceeded £ 574 million (Birch, et al., 2006).

2.4.2 EUnetHTA Core Model

As HTA processes were increasingly used in European countries to inform decision and policy making in the healthcare sector, the EU and Member States in 2004 expressed the need for a sustainable European network for HTA, thus EUnetHTA was established to respond to this necessity. The European Commission and Member States co-founded the three year project (2006-2008) with the aim to develop a information network to spread health decision making models and support policy decisions, leading to the establishment of a partnership which involves 64 organizations around the world.

The strategic objectives of the EUnetHTA project were to:

- Reduce duplication of effort in order to promote effective use of resources;
- Increase HTA input to decision making in Member States and the EU in order to increase the impact of HTA;
- Strengthen the link between HTA and healthcare policy making in the EU and its member states;
- Support countries with limited experience of HTA.

The scientific work took place in separate Work Packages (WPs), which were characterized by these features and major results (EUnetHTA, 2008):

WP	Description	Results
1. Coordination of the project	Manage and implement the project	A well functioning network of partner and colleagues from HTA agencies, research institutions and health ministries
2. Dissemination of the project	Ensure that results and deliverables are made available to target groups	A well functioning Information platform
3. Evaluation of the project	Verify if the project is implemented as planned and reaches the objectives	Internal evaluations that helped to adjust work plans
4. Testing collaborative production of HTA information for national adaptation and reporting	Develop systematic networking to jointly produce HTA information for national reporting while piloting the application of EUnetHTA tools	A comprehensive, evidence-based and validated common framework (HTA Core Model) applied to medical and surgical interventions, and to diagnostic technology
5. Applying the HTA Core Model for Rapid Assessment for national adaptation and reporting	Conduct fourteen pilot rapid assessments containing structured core HTA information based on the HTA Core Model	An adaptation toolkit and a guidance document composed of checklists and resources addressing relevance, reliability and transferability of data
6. Information Management Infrastructure and Services	An efficient Information Management System is the central building block of the EUnetHTA network	The “Health Technology Assessment and health policy-making in Europe” document and a web-based stakeholder forum
7. Methodology development and evidence generation: Guidelines and pilots production	A database containing information on evidence generation on new technologies is actively used to foster cross-border collaboration on shareable data collection for required additional studies	Web-based tools for information sharing on the monitoring of new promising technologies and information service on emerging technologies

8. Maintenance of HTA Core Model infrastructure to support shared production and sharing of HTA information	Development of Online Tool & Service to support information production	A handbook on HTA capacity building
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Figure 2.10 - The EUnetHTA Work Packages

This section is aimed at describing the WP4, i.e. the development of the HTA Core Model.

One important property of the Core Model pertains to ethical aspects, which have a broader application within HTA: in fact, the assessment themselves should be designed in order to consider and respect ethical principles, regarding for instance morally relevant reasons for performing or not performing a HTA on a certain intervention, the identification of interests of producers of technologies, the choice of end points in the assessment, the scope of the HTA and choice of research methods.

The Core Model tries to define and standardize elements of an HTA, by tackling two problems: on the one hand, in order to detail the contents of an HTA report and reduce their differences across national and regional documentations, it suggests what kinds of information should be included in an ideal comprehensive assessment, and on the other hand the Model enables future international, systematic and even automated use of HTAs through a shared and detailed structure, thus being used for educational purposes within HTA as well.

The current first version employs nine *domains* which characterize a complete healthcare technology evaluation:

1. Health problem and current use of the technology (implementation level)
2. Description and technical characteristics of the technology
3. Clinical effectiveness
4. Safety
5. Costs and economic evaluation
6. Ethical analysis
7. Organizational aspects
8. Social aspects
9. Legal analysis.

Regarding the ontology of HTA, the basic unit of the model is an *assessment element*, which is a piece of information which describes the technology or the consequences or implications of its use (for instance a clinical outcome), or the patients and the disease for which it is applied. An element may

be both context-independent and very important, so that transferability to other contexts is attested.

As stated above, a *domain* is the wide framework within which the technology is considered, a certain point of view about use, consequences and implications of any technology. One domain is divided into several *topics*, which address more specific areas of consideration within any domain, such as regulatory status related to current use of the technology or life expectancy related to clinical effectiveness. One topic typically consists of several *issues*, but may also contain only one issue, which is an even more specific area of consideration within any of the topics. Issues are expressed as questions, which may be similar to research questions within scientific studies.

As it can be seen in the figure below, the combination of a domain, a topic and an issue defines a single *assessment element*, and each element is described in more detail in an *element card*. Element cards are not specific to any technology, thus providing both information regarding clarifications, data sources and references, and guidance on how to conduct research, i.e. how to answer research questions. Examples of a *element card* and of an *assessment element* are provided in Annex B.

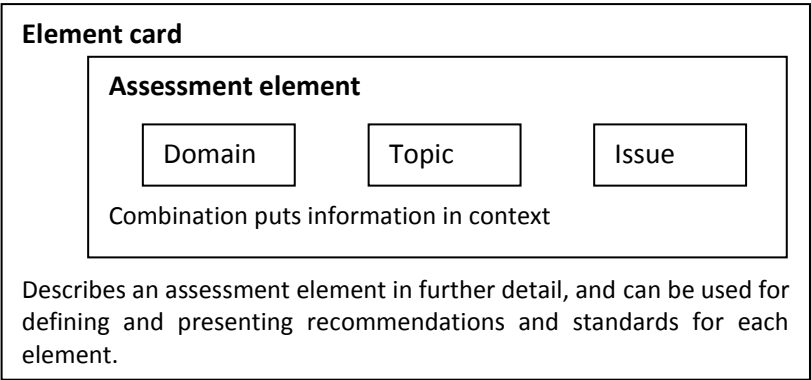


Figure 2.11 - Relationship between assessment elements and element cards

The inclusion of an element in the Core is a function of two basic characteristics, which are not necessarily dependent on each other, its importance and transferability (see Core Matrix below). The first factor guarantees that the provided information is robust and significant from the viewpoint of HTA, while the second one entails that if the information is fully or partly transferable, it may provide valuable input beyond its original production location. As it can be seen in the figure, category “borderline” was included in the matrix during the project period, but then it was removed from the final version of the model: the rationale for inclusion is driven by usability of the information across national borders of other contexts (see example of *Important* element, *Not* transferable -> Not core).

CORE MATRIX		Importance		
		<i>Optional</i>	<i>Important</i>	<i>Critical</i>
Transferability	<i>Complete</i>	Borderline -> Not core	Core	Core
	<i>Partially</i>	Not core	Borderline -> Not core	Core
	<i>Not</i>	Not core	Not core	Borderline -> Not core

Figure 2.12 - The Core Matrix

The HTA Core Model was built within WP4 by several working groups called “teams”, each one of them focusing on one domain. The teams were first requested to agree on a definition of the domain they worked on, providing some indications about possible overlaps with other domains, and subsequently lists of topics and issues were requested. After a consensus process, the two key characteristics assigned to elements were defined.

The HTA Core Model can be utilized in two ways for conducting HTA: *Core HTAs* are comprehensive assessments that guide researchers in selecting which aspect of technology or its use they could study, while taking into account the multidisciplinary nature of health technology assessment: a summary of the findings of each domain, drawing together evidence gathered during the process, is thus provided; the second type of use is a more “liberal” selection and use of various assessment elements, perhaps from only one or few of the domains. Both of them constitute a collection of *Structured HTA Information* that can be utilized when performing local HTAs: however, it’s important to highlight that Core HTAs refrain from giving recommendations of the use or non-use of technologies (EUnetHTA, 2008).

2.4.3 EVIDEM Framework

The EVIDEM (Evidence and Value: Impact on Decision Making) Collaboration is a non-profit Canadian organization aimed at bringing together diverse perspectives and expertise in order to promote public health by supporting transparent and efficient healthcare decision making through systematic assessments and dissemination of evidence of healthcare interventions, for the public benefit. Indeed, its key principles are:

- **Collaboration** between all stakeholders to foster constructive communication;
- **Access** to best and relevant evidence on healthcare interventions to facilitate knowledge transfer to those making decisions at micro, meso and macro levels;
- **Transparency** of evidence and values underlying decisions to facilitate understanding by stakeholders;
- **Consistency** in deliberations and decision making.

Thus, the EVIDEM framework has been developed in order to help HTA and efficient healthcare decision making with a tool which facilitates the systematic and explicit consideration of multiple

factors that may influence decisions, the Multi-Criteria Decision Analysis (MCDA). In this decision model, all features which affect a certain choice are defined as “criteria”, then decision makers assign weights to each criterion according to its subjective importance, and secondly score performances of each healthcare intervention with respect to each criterion, a step that prompts explicit consideration of the advantages and disadvantages of each option and fosters discussion within the decision making group (a further description of this decision model, with its organizational implications, is provided in the next paragraph) (Goetghebeur, et al., 2012).

Although MCDA may be perceived as not intuitive and potentially usurping decision making authority, it facilitates dialogue and forces decision makers to think hard about what, why and in what context they value. As shown in the figure below, the EVIDEM framework is designed to provide a Core MCDA Model adaptable to the context of decisions (thanks to the Contextual Tool), combined with a “by-criterion” HTA report methodology which arranges synthesized and good quality evidence at the criteria level. This approach facilitates knowledge transfer and enhances communication of the decisions, thus establishing a prioritization for interventions.

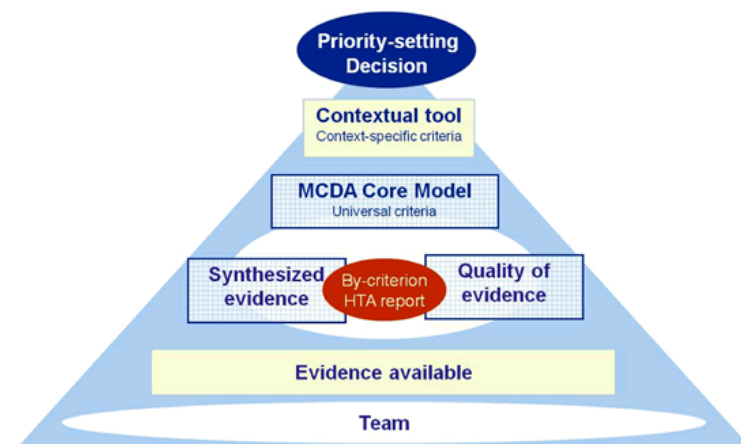


Figure 2.13 - Overview of the EVIDEM framework

Criteria of the framework were defined to fulfill the MDCA requirements of completeness, nonredundancy, operability, and mutual independence, furthermore they emerged from an extensive analysis of literature and decision making processes. On the one hand, the MCDA Core Model defines the 15 universally normative criteria, while on the other hand the Contextual Tool is used as a guide to tailor the framework to the context of decision making, including 6 generic criteria, 2 of which regarding contextual normative, and 4 feasibility, as depicted in the summarizing table in the following page. It is a means to capture non quantifiable considerations that may affect the overall appraisal (EVIDEM Collaboration, 2011).

MCDA Core Model	Contextual Tool
What should we do? Which interventions contribute the most to health and sustainable systems?	What is our context and what can be done?
Disease impact D1: Disease severity D2: Size of population Context of intervention C1: Clinical guidelines C2: Comparative interventions limitations Intervention outcomes I1: Improvement of efficacy/effectiveness I2: Improvement of safety and tolerability I3: Improvement of patient-reported outcomes Type of benefit T1: Public health interest T2: Type of medical service (cure) Economics E1: Budget impact on health plan E2: Cost-effectiveness E3: Impact on other spending Quality of evidence Q1: Adherence to requirements of the decision making body Q2: Completeness and consistency of reporting evidence Q3: Relevance and validity of evidence	Contextual normative criteria – ethical principles of utility and fairness Et1: Utility – goals of healthcare Et2: Fairness – population priority and access Contextual feasibility criteria – aspects to be tailored to the specific context Et3: Efficiency – opportunity costs and affordability O1: System capacity and appropriate use of intervention O2: Political/historical context O3: Stakeholder pressures/barriers

Figure 2.14 - MCDA Core Model and Contextual Tool

Thanks to the framework, healthcare interventions can thus be ranked onto a value scale, and recommendations are given on what should be done, according to the context itself which can modify the ranking and affect selection of investments and disinvestments.

In one of its first tests, the decision framework was submitted to a group of representative healthcare stakeholders who appraised 10 medicines as case studies from six therapeutic areas, thus the study design involved these three phases (Goetghebeur, et al., 2012):

- Development of “by-criterion” HTA reports: in this phase, investigators performed an extensive review of the literature and synthesized data to inform each of the 15 decision criteria organized into the MCDA matrix. If head-to-head clinical trials were lacking, data from trials of key comparators were also synthesized and presented. In addition to publicly available data, proprietary data were provided by a manufacturer. Most critical data were then reported in standard comprehensive tables which summarized study information and results: in particular, regarding the quality of evidence and uncertainty, a critical analysis of studies and available evidence was performed, then commented and graded on a 4-point scale from 0 (no data) to 3 (no gaps/no critical issues) by two investigators, who separately discussed their findings and reached consensus.
- The appraisal group was designed to include stakeholders from 6 different categories: specialists, general practitioners, nurses, pharmacists, policy decision makers, and health

economists/epidemiologists. Patients or patient groups were not included in the exploratory pilot study, but were involved in subsequent studies applying the framework.

First of all, during the workshop participants weighted the importance of each criterion of the MCDA Core Model, independently from the interventions to be appraised, so that capturing their individual perspective was possible. A 5-point scale was selected (an example is represented in the figure below), where 1 represented the least and 5 the most important criteria.

Criteria	Weights
	Low ← → High
Example Disease severity	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Figure 2.15 - Example of weighting scale

Since not all the interventions are equal, and not all medicines are the same, the second step consisted in measuring their performances by scoring each criterion on a 4-point scale, where minimum was 0 and maximum was 3, as it can be seen in the figure below.

Criteria	Scoring scale
Example Disease severity	☐ 0 – not severe ☐ 1 ☐ 2 ☐ 3 – very severe

Figure 2.16 - Example of scoring scale

Technically, MCDA estimates of perceived value V were calculated with a linear model: the weights W_x were normalized (i.e. distributed across the 15 criteria to sum up to 1 for each participant), and the scores S_x were standardized by dividing them by the maximum score 3. Thus V is expressed on a scale from 0 to 1, resulting from combined normalized weights and scores for all decision criteria, as represented in the formula:

$$V = \sum_{x=1}^n \left(\frac{W_x}{\sum_{x=1}^n W_x \times \frac{S_x}{3}} \right)$$

For an estimate close to 1, an intervention would approach the ideal, providing improvements on quality of life and benefits in terms of healthcare savings.

- Feedback on the approach was collected during structured discussions which tackled key topics regarding: weighting process, additional decision criteria, HTA content, scoring process, MCDA estimate, and potential applications in professional environments.

The strengths of this model mainly regards its utility to decision makers, thanks to its adaptability to local contexts and to its combination of quantitative and qualitative aspects; the second aspect is

referred to the pragmatic, user oriented and modular methodology, which is available and open for users, thus providing a tool for developing and knowledge sharing. The weighting process is a means of stimulating reflection on committee members, while aspects not included in the MCDA Core Model, such as political and historical context or priorities of funding bodies, emerge and potentially carry sufficient extent to change results of an appraisal that was just based on the scientific and quantitative features (Goetghebeur, 2011).

On the contrary, challenges to overcome regard mostly the perception of complexity of the model and the risk of using the MCDA itself as just a formula, rather than as a support to decision making and priority setting, thus affecting data reliability and stakeholders' beliefs: in fact, in some cases participants indicated that they provided low scores because they deemed the data insufficient or not valid. Furthermore, scoring scales expressed by subjective individuals may not be linear, which undermines the basic assumption of the decision model itself. Another point regards the limited MCDA expertise in healthcare, which can be overcome only if collaboration among stakeholders is promoted and transparency is enhanced by facilitating communication of data needs and decision rationales. In conclusion, besides the methodological development and improvement, field adaptation and implementation are feasible by creating a community of multi-criteria practice and a collaboration which continuously optimize the open source framework and toolkit.

2.5 Innovative Research Streams in HTA

At this level, a proper search was undertaken on the database SciVerse Scopus in order to define in depth the context and main features of both the Multi-Criteria Decision Analysis and the Programme Budgeting and Marginal Analysis, with additional keywords such as "Health Technology Assessment OR HTA", "priority setting", "ranking OR weights AND scores", and "uncertainty OR health risk". In particular, this search was needed on the one hand to clearly distinguish why and what for MCDA is used, and how stakeholders behave when dealing with it, while, on the other hand, how PBMA could complement the former methodological approach. As previously described, the choice of the most appropriate methodology to use for decision making is still controversial, thus there is no definite and robust evidence about which procedure performs best during the priority setting phase.

2.5.1 Multi-Criteria Decision Analysis (MCDA)

Strategic technology management and priority setting are increasingly dependent on budget constraints, thus decision making requires evidence to ask for approvals and reimbursement of certain interventions. The goal of this literature review was to depict the role of Multi-Criteria Decision Analysis (MCDA) as a means of supporting judgments on appropriateness and consistency

related to technologies of interest, by providing a model which can be easily and transparently incorporated into stakeholders' daily perspectives.

As the National Health Service imposes revision of healthcare organizations' budget plans, the need for economic sustainability is connected to legitimacy and fairness of decision making. When specifically determining the disinvestment of a not profitable or obsolete technology with a new replacing one, which will bring further benefits, a method that has been developed on this purpose is the Programme Budgeting and Marginal Analysis, discussed throughout the next paragraph.

From the outset, MCDA was thought as a methodological approach which could embrace different relative points of view, by defining relevant and exhaustive criteria which characterized decision makers preferences. On the one hand, this technique can solve conflicting interests on local level decisions, while on the other hand it has the capability of involving experts with different geographical and institutional backgrounds, in order to provide a more exhaustive overview, as the EVIDEM Collaboration aims at.

Whilst clinical research activities are fundamentally "truth-driven", policy making within the scope of benefit-risk assessments, for instance, is basically decision-driven, thus a pure mathematical method is not appropriate to involve all the facets of a choice involving the healthcare domain. The conceptual framework of MCDA is usually made of these steps (Mussen, et al., 2007):

1. Establishment of the decision context: as any technology is different from other ones, a separate assessment should be conducted for each intervention or indication, if we are dealing with medicines, for example;
2. Identification of the options to be appraised: in this case, both the intervention' itself and comparators' impacts are to be taken into account by decision makers;
3. Identification and organization of the criteria: first of all, the criteria for assessing the consequences for each option should follow these characteristics:
 - a. Value relevance: each criterion is relevant for and linked to the final decision.
 - b. Understandability: stakeholders have a shared understanding of each criterion.
 - c. Measurability: MCDA requires a certain degree of measurement of the performance of each option against certain specified criteria.
 - d. Non-redundancy: as a general rule, it is better to combine similar criteria in a single concept.

- e. Judgmental independence: it must be assured that all criteria are mutually preference independent, i.e. scores that are assigned on one criterion are unaffected by the scores on other criteria.
 - f. Balancing completeness and consciousness: all critical aspects of the problem must be captured, but also the model has to be concise and keep the minimum required level of detail.
 - g. Operability: the model has to be usable with reasonable effort.
4. Assessment of the performance of each option against the criteria: according to the description of the consequences of each option against criteria, every option must be scored, in line with their performance, on a scale of measurement, where two reference points are maximum and minimum, and other numerical values are allocated between them; when finding a measurable attribute which captures a criterion is not possible, *qualitative value scales* are constructed, or *direct rating of the options* can help in specifying the value of an option in relation to certain reference points. Often the method of pair wise comparisons of the options is used to establish the options on the scale and to check consistency of the judgments;
 5. Assignment of a weight to each criterion: their relative importance to the decision is expressed by a judgment on a preference scale, usually from 0 to 1 or from 0 to 100, in order to determine the level at which every criterion takes part in the achievement of the overall objective;
 6. Calculation of the weighted scores: the weights are normalized, so that the total sum of all weights equals 100, then for each option the score of each criterion is multiplied by its normalized weight; thus, the overall preference score for each option is simply the weighted average of its scores on all the criteria.

Letting the preference score for option i on criterion j be represented by S_{ij} and the weight for each criterion by W_j , then for n criteria the overall score for each option S_i is given by the following equations:

$$S_i = W_1S_{i1} + W_2S_{i2} + W_nS_{in} = \sum_{j=1}^n W_jS_{ij} \text{ with } \sum_{j=1}^n W_j = 100$$

7. Conduction of a sensitivity analysis: in the end, this typology of analysis should be carried out to investigate whether the conclusions reached in step 6 are robust or if they are sensitive to changes in aspects of the model, by exploring the impact of assigning more or less weight on indifferent criteria.

As an example of its application, the MCDA model has been used through the EVIDEM decision making framework to growth hormone (GH) for Turner syndrome (TS) patients in Canada. Applying the framework enabled decision makers to detect significant data gaps and the importance of aligning research questions with data needs to truly inform decision. Panelists estimated the value of GH for TS at 41% of maximum value on the MCDA scale, with good agreement at the individual level and large variation across panelists. Main drivers to this panel specific value were “Improvement of efficacy”, “Disease severity” and “Quality of evidence”. On the other hand, ethical considerations on utility, efficiency and fairness as well as potential misuse of GH had mixed effects on the perceived value of the treatment. This experience shows how this model supports systematic consideration of all components of decision and available evidence for greater transparency (Goetghebeur, et al., 2010).

Moreover, the manner in which preferences of decision makers are combined across individual criteria, allowing also for inter-criteria comparisons, separates the different MCDA techniques. The different MCDA approaches can be broadly classified into three categories (Thokala, 2011):

- *Value measurement models*: the degree to which one decision option is preferred to another is represented by constructing and comparing numerical scores (overall value). The scores are developed for each individual criterion initially and aggregated into higher level value models. Almost everyone who has suggested using MCDA methodology for health technology assessment suggested this approach for its simplicity, however it is not without its constraints, being a compensatory method: in fact, poor performance on a criteria can be overcome by doing well in other criteria depending on the weights and partial value functions, thus misleading the overall judgment. Also, the strict theoretical basis of this approach means that considerable caution needs to be taken to satisfy the preferential independence of criteria and the corresponding tradeoffs of different weights. Program budgeting and marginal analysis (PBMA) and analytic hierarchy process (AHP), another widely used MCDA technique, are also based on this value measurement modeling approach.
- *Outranking models*: the alternatives are compared pair wise, initially in terms of each criterion, in order to assert the extent of preference for one over the other for that criterion. The preference information across all criteria is aggregated to establish the strength of evidence favoring selection of one alternative over other. This approach is not widely used but could also be an appropriate alternative for MCDA in HTA as it is based on direct comparison of the key characteristics of the drugs/treatments.

- *Goal, aspiration or reference level models*: this approach involves derivation of the alternative(s) which are closest to achieving the pre-defined desirable (or satisfactory) levels of achievement for each criterion. Value based pricing, used to set the prices of drugs/treatments such that the ICER is under the relevant cost-effectiveness threshold, could be implemented using this MCDA approach, provided the definition of “value” is clearly identified by the health organizations such as NICE or NHS.

Besides the structured model, an important feature of MCDA is the ability to represent the opinion of preference configurations of various stakeholders in order to build a consensus: in the absence of a transparent tool to reflect preferences in an objective manner, disagreements and trade-offs become difficult to resolve because there is no way to show if and how differences translate in different choices (Fazil, et al., 2008). Thus, referring specifically to HTA, its priority setting process should be strongly embedded into the organizational context, so that an advisory panel, which comprises health personnel, policy makers, finance and information staff, and community representatives, can have the important role for decision making and recommendations for reallocating resources on the basis of MCDA results. As concluded in a survey conducted by the INAHTA in 2006, the involvement of “consumers” (i.e. including patients, carers, long-term users of services, organizations representing consumers’ interests) in the assessment and decision making processes within HTA agencies “broadens the perspective of those assessments and of the advice provided to decision makers”. Moreover, as previously stated, patients can be involved at various levels in healthcare decision making, that are micro, meso and macro levels, as experts on their own health providing information to healthcare professionals, broadening, in this way, the ethical perspective of policy making (Danner, et al., 2011).

However, although ethical evaluation helps stakeholders realize consequences of implementing a healthcare intervention, only 47% of INAHTA member organizations reported including ethics in their assessments: only thanks to the combination with stakeholder involvement, these elements can lead to effective legitimization of healthcare decisions and to the concept of “accountability for reasonableness” (A4R). The A4R framework is grounded in democratic theory, and engages fairness principles with healthcare institutions only when decisions are made accessible for public, priority setting is relevant in the specific context, there’s a way to appeal for these decisions and their rationales, and these first three conditions have to be warranted by voluntary or regulatory means. Only by forming a public record of decision and the reasons behind them, the reasoning process itself, applied to priority setting, can be improved over time (Gruskin, et al., 2008).

When the ethical principles of utility, efficiency and fairness are in conflict, MCDA becomes a fundamental vehicle not only for making decisions, but, most importantly, it becomes a framework to think and talk about a decision – a decision language. In fact, in the very moment that each one expresses himself in a language well know and shared by all, it's possible to define the concept of process ownership, which relates to listening of others' opinions, respect for deadlines and consideration received for provided information, awareness and change of performances factors, knowledge sharing and team working.

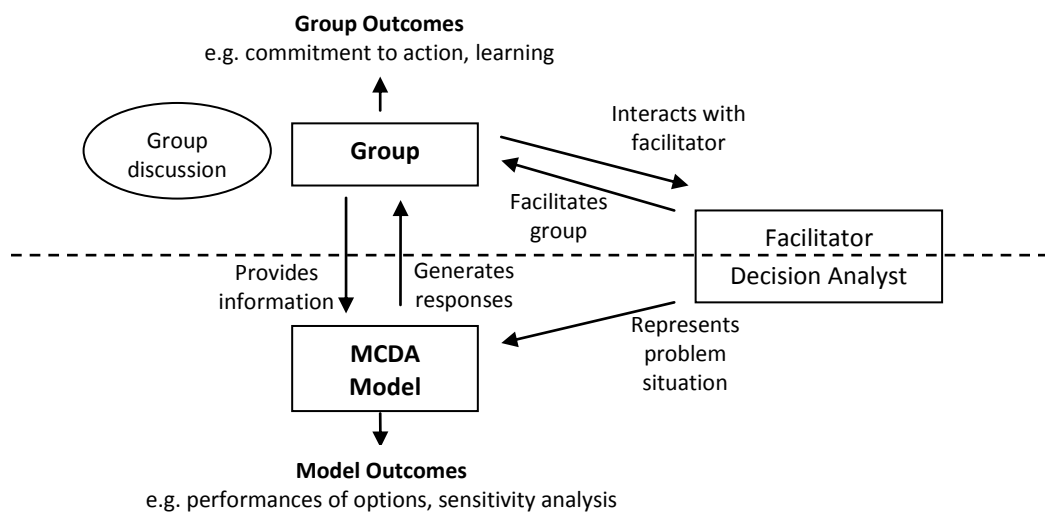


Figure 2.17 - Example of Facilitated decision modeling

As depicted in the above figure, the ideal decision framework suggested by (Montibeller, et al., 2011) involves a close interaction between the Group, which makes decisions, and the Model itself, which provides outcomes to be critically elicited. A facilitator who both enhances effective communications among participants and is able to tabulate the problem situation provides the proper balance between legitimacy and transparency, by managing group dynamics and engage decision makers.

By sequentially meeting, panelists have the opportunity to shape their deliberations through mutual learning, which injects a sense of empowerment and strong feelings of ownership over the results: being a stakeholder means both affected and affecting the problem, and at the same time participating in the process of formulating and solving it, thus principles for deliberations have to be clearly defined from the outset;

- Transparency and auditability: as already stated, being involved in the whole process contributes to more ownership for policy makers, furthermore a structured appraisal has to represent all explicit reasons for a certain perspective about an issue;
- Timeliness and cost: when many stakeholders' interests are at stake, and when uncertainties and variability, as well as divergent ethical positions, regard to the amount of time to make

the decision and the budget constraint are prerequisites for acceptance and commitment as well (Burgess, et al., 2007).

On the other hand, one issue to deal with is the participation or non-participation of stakeholders to the problem formulation and solving process. A first category of reasons is linked to the quality of the decision, i.e. its quality and rationality requirements, the sufficient amount of information or the robustness of problem structure; the second point refers to the socio-political dimension, which takes into account the level of acceptance of a certain decision by subordinates, the shared organizational values in solving the problem, and the conflicts to face during consultations. There will be stakeholders expected to support the decision making process, those expected to resist it and those who are likely to be indifferent: the degree of support is thus defined by each individual's approach. Besides the value of transparency in cases where individuals have some control over the evolution of the situation, one interest point, which links the stakeholders' approach to MCDA, regards the concrete legitimacy and implementability of the solutions obtained with the multi-criteria method, which strongly affect their behavior (Banville, 1998).

In conclusion, the Multi-Criteria Decision Analysis can be considered as a means to overcome barriers to priority setting and to develop a scientific model which provides evidence to assist decision makers in making complex judgments. This technique is basically aimed at making opinions emerge through dialogue and setting options consistent both among each other and with stakeholders' objectives. Therefore, the greatest strength of MCDA is its continuous learning mechanisms of individuals about their priority setting preferences, which is connected to another methodology which merges knowledge generation with action, called Participatory Action Research (PAR). A distinctive feature is that in this case research is conducted by and for those who are the end users of the research itself, being designed as context specific, to address specific issues identified by stakeholders, and its results are used to directly solve those problems (Peacock, et al., 2009) (Patten, et al., 2006).

Overall, by combining internal commitment, thanks to capacity building and acknowledgement of change as an incremental process, and encouragement of partnerships, the sustainability of priority setting in Health Technology Assessment is more and more strengthened in its continuous process of eliciting evidence and value in a participatory and significant manner specific to the context.

2.5.2 Programme Budgeting and Marginal Analysis (PBMA)

The challenge of priority setting in health organizations reflects the need for decision makers to iteratively refine current decision processes and better deal with the problem of resource allocation,

such as the MCDA model already seeks for. However, the distribution of resources tends to be conducted according to historical or political criteria, which can lead to sub-optimal use of the limited and scarce funds.

The Programme Budgeting and Marginal Analysis (PBMA) is an approach for setting health priorities used mainly in United Kingdom, Canada, Australia and New Zealand, which is based on principles of economic evaluation, but with a more pragmatic “modus operandi” applicable at different levels of health organizations. Its framework comprises two distinct tools: on the one hand, programme budgeting splits overall budgets into programs of care rather than individual procedures and supplies, while on the other hand marginal analysis evaluates the effects of changes to the programs in terms of costs and outcomes. Anyhow, it’s important to highlight that PBMA has been thought as an input to the decision process, and not as the decision itself (Wilson, et al., 2009).

As a technique aimed at bridging medical and managerial cultures, opportunity costs here are associated to different costs and benefits of various healthcare activities at the margin, i.e. the benefits gained from an extra unit of resources or benefit lost from having one unit less. Thus, five questions about resource use can be split among the two principles (Ruta, et al., 2005):

- PB: What are the total resources available? On which services are these resources currently spent?
- MA: What services are candidates for receiving more or new resources (and what are the costs and potential benefits of putting resources into such growth areas)? Can any existing services be provided as effectively, but with fewer resources, so releasing resources to fund items on the growth list? If some growth areas still cannot be funded, are there any services which should receive fewer resources, or even stopped, because greater benefit would be reached by funding the growth option as opposed to the existing service?

Moreover, this framework is broken down into seven stages, which are designed to provide a transparent and explicit framework for priority setting (see figure 2.18 in the next page) (Peacock, et al., 2009):

1. Determine the aim and scope of the priority setting exercise	Determine whether PBMA will be used to examine changes in services within a given program or between programs.
2. Compile a “program budget”	Resources and costs of programs will need to be identified and quantified, becoming a program budget when combined with activity information.
3. Form a “marginal analysis” advisory panel	A panel of 8-30 people, made up of key stakeholders, is formed to advise the priority setting process.
4. Determine locally relevant decision making criteria	Elicited from the advisory panel’s expertise, referring to national, regional and local objectives, and specified goals of the health system and the community.
5. Identify options for service growth, resource release from gains in operational efficiencies and resource release from scaling back or ceasing some services	The program budget, along with information on decision making objectives, evidence on benefits from service, changes in local healthcare needs and policy guidance, are used to highlight options for investment and disinvestment.
6. Evaluate investments and disinvestments	Evaluate in terms of costs and benefits and make recommendations for funding growth areas with new resources.
7. Validate results and reallocate resources	Re-examine and validate evidence and judgments used in the process and reallocate resources according to cost-benefit ratios and other decision making criteria.

Figure 2.18 - Stages of PBMA

In particular, as a common feature with MCDA, being the advisory panel composed of a mix of clinical personnel and managers, all different stakeholders’ values are represented, made explicit thanks to training and communication, and shared with an accepted vision.

International experiences have highlighted the central role of advisory panels in setting priority, due to its role in making recommendations to better meet organizational or health system objectives. In this case, there are ethical considerations to take into account, since efficiency and service reductions can result if decision makers have a genuine interest in improving the health of the population: anyway, fairness and openness in the process always improve the perceived credibility of decisions, thus helping to mitigate practical problems arising from disinvestment and resource releases (Peacock, et al., 2008).

While PBMA is seen as a useful tool, difficulties have arisen in progressing towards the identification of options for disinvestment, in fact there are four barriers to overcome:

- Budgetary pressure: when budget constraint is poorly specified and/or treated as a decision variable, PBMA fails to effectively link questions about investment and disinvestment, and this is more visible in periods of rapid expenditure growth, when commissioning new investments remains feasible independently of any disinvestment and resource release from existing services.
- Scope of the program budget: where the program budget spans a wide range of health services, delivered in different settings and to diverse patient populations, direct

redeployment of resources may be difficult to achieve, and the breadth of the program budget may itself prove a barrier to disinvestment.

- Advisory group: when members are selected for their expertise, rather than to represent the interest of stakeholders, it's more difficult for them to set aside their sectional interests while developing impartial "wish lists" and "shift lists", which advocate in favor of investing in their budget area and disinvesting in other ones.
- Incentives: since the culture of healthcare has been rewarded as "overspending, whereby individual programs get budgeted what was spent, instead of being rewarded for staying within budget", and with the risk that released resources are reclaimed from fund-holders as their productivity dividend, rather than being reallocated to fund investment options within the program budget, advisory groups seek first for an increase in their budget allocation or shift costs to other programs.

Thus, actions to reorient PBMA towards disinvestments refer to defining broadly enough programs to include all feasible areas of service expansion and contraction, but, within that program budget, investment proposals have to be linked to disinvestment ones with relatively similar input requirements; regarding budget constraints and advisory groups, in order to avoid opportunist behaviors and maximize community health or welfare, attributes of benefits and their relative weights may be more directly assessed by citizens' juries or deliberative polling than by physicians, hospital managers or consumer representatives. Finally, financial incentives, whereby clinicians are empowered to reinvest a portion of resources released back into their services, can encourage participation (Mortimer, 2010).

Throughout the world, many PBMA experiences have developed during the last years: for instance, in Britain Primary Care Trusts (PCTs) are the channel for most NHS resources, while it's necessary for them to keep track of all expenditures in all the areas of interest, by communicating long-term purchasing intentions. In fact, NICE recently indicated a focus on appraisals of not only technologies for investment but also areas for disinvestment. In Canada, after the 2008 global economic crisis, the extreme pressure on public sector spending moved a commitment to consider options for resource reallocation, thus a project was established to develop a plan to address a forecasted deficit of approximately \$ 4,65 million for fiscal year 2010/11 in the Vancouver Communities division of the Vancouver Coastal Health Authority. Assessment criteria linked to priorities of the health authority regarded strategic alignment to mandate, health impact on population, organizational impact on workplace environment, innovation and knowledge transfer. The results obtained thanks to the

PBMA implementation enabled the organization to meet the deficit and to infer conclusions for three major themes (Mitton, et al., 2011):

- Training was focused, direct and relevant for decision making, thus it was important when using real life examples in demonstrating the potential impact of PBMA on changes to services;
- Implementation improved the decision making process, as previous resource allocation procedures relied on historical patterns and/or politics;
- Future use regarding knowledge sharing across organizations, which do not tend to work together, but whose decisions impact on each other.

The Australian experience focuses more on the advantages of use of expert panels, who discuss of the meaning of benefits in order to gain a clearer understanding of different dimensions of advantages in each particular context. By making a defined distinction between levels of health gain, equity, and empowerment, in terms of enhancing individuals' and communities' ability to take control of their lives and the environment around them, it is crucial that panel members have the same, shared understanding (Peacock, et al., 1997).

In conclusion, the effective use of PBMA may face barriers due to reluctance from doctors to accept loss of funding if their services are judged to have low marginal benefit, lack of trust between stakeholders, advisory panels lacking health economic knowledge and/or allocation experience, politics preventing program evaluation; thus, in order to move towards a shared and interdisciplinary education, besides the financial incentives which can encourage participation, the process starting point is a joint cooperation, making sure that a finite amount of resources is deployed in a way that maximizes health gain for the community.

2.6 Literature Gaps

From the review and analysis of literature, many questions arose about how Health Technology Assessment can be actually performed in practice. In fact, even though different experiences and purposed decision models have been designed, relevant issues still have to be answered. These topics basically refer to how decisions made at macro level could be transposed at local level, to which decision making instruments are more appropriate in order to best conciliate available information with timeliness, and to the role of stakeholders and their related involvement into the whole process.

First, as shown throughout the previous paragraphs, practices of different international experiences are described at their higher degree, without deepening a definition of steps to be implemented and

of impacts to be faced on decision making at micro level. For instance, this missing link is highlighted in the United Kingdom by the absence of guidance on how managers and doctors are to commission effectively health priorities and by the relatively poor record of the NHS in implementing evidence from economic appraisals at the local level; clinical evaluations are not sufficient to make a decision, furthermore surveys in the United Kingdom, Canada, and Australia have shown that local managers and doctors have limited awareness of economists' tools that could help them to set priorities, although they would prefer to work with such tools (Peacock, et al., 2008). The NICE three-tier approach is limited to publishing a final agreed appraisal position which will be endorsed in its technology guidance, but a further determination of how recommendations are to be interpreted and contextualized is not provided. Also the EUnetHTA, which embraces the European background, has up to now created a robust network for information sharing and upgrading, but this still impacts on the country dimension, rather than on a more specific evaluation of specific possible needs of local authorities. On the other hand, the EVIDEM Collaboration showed examples of peculiar priority setting cases, while trying to actually provide advices for single implementation of its framework; however, as the "fine tuning" process is ongoing, organizations, which intend to take advantage of this useful decision making tool, should also have a sufficient detachment to adapt it to their specific context and to avoid its drawbacks.

The second point is related to how decision making models are designed: as formerly described, different indicators are taken into account in order to determine a final term of comparison for priority setting of interventions or technologies; nevertheless, it is not clear whether these results represent a means or a target for prioritization, as many instances refer them as minor tools that have to be deeply discussed by reference stakeholders prior to the final decision. Furthermore, while investigating the Multi-Criteria Decision Analysis, for instance, reported experiences refer that core criteria for evaluation are defined, but it is still difficult to document those ones which lie outside the clinical background, i.e. thorough economic analyses, context-related data or organizational issues. Thus, this is reflected on associated weights and scores: not only who and thanks to which rationale has to express them have to be well-clarified, but also how appropriate scales and rating definitions are to be systematized, as the linear additive method itself should be properly used in order to provide reliable results. More specifically, the MCDA is a compensative model, thus purposed balances may incur when a criterion performs better, while another one worse: procedures for sensitivity analyses may be more difficult in a real context, which is different from a pure exercise-based background, as first model implementations are ongoing in this field.

The concept of factual implementation of these models is linked to the frequent question about how much is the time needed to ponder a decision, as literature doesn't report average information about this topic: thus, it's important to clarify how flexible and adaptable are implemented procedures in order to meet possible consequences of late decision making, and experiences have to be provided in order to determine a general framework to take as reference point. Moreover, timeliness has to be provided with proper stakeholders who are directly focused on the issue of interest, and this should be connected with a consistent composition of the evaluation group, which has (potentially) equal voice on the final decision.

The third object of investigation is related to the organizational structure of HTA, as a specific definition and delimitation of roles is still controversial according to different decision making procedures described in literature: the first question regards whether the same composition of evaluation groups is maintained at different steps, or, otherwise, which disciplines participate to which single phases, then how to conciliate decision making with different perspectives to be taken into account. In fact, these concepts point out the question of whether the clinical base is sufficient for comprehensive judgments and subsequently which specialty professionals are further needed to complete both the overview on the technology at discussion and the final indicator for prioritization. Many experiences speak about the achievement of a final consensus, but the way through it should be described and appropriate methods should be embraced to robustly support and give reasons for qualitative opinions. For instance, few is reported about non-clinical or non-economic roles, thus there is uncertainty about equity of access to advisory committees, appropriate verification of conflicts of interest, or pressures of different stakeholders which could possibly occur during the whole process; then, effects of decisions on public consultations are not stated, generating doubts on whether impacts of choices are preventively assessed or not.

Furthermore, participants to advisory panels represent key domains for technology priority setting, but sometimes they may have been chosen for their expertise on policy making, rather than on the topic of evaluation itself. Thus, the concept of impartial expression of opinions and judgments represents a significant point for legitimization of decision making. Afterwards, this should be consistent with a well-defined level of communication and feedback between different stages, that often are represented as "non-speaking" boxes. Finally, what are the proper instruments for stakeholders' engagement, if necessary, have to be clarified, hence detailing which are the how-to and what-for steps for creating cohesiveness.

3. Methodology

The present study followed different phases of analysis in order to clearly define how the current practice is performed and what possible improvements are applicable in the long run to the whole process. Thus, this chapter will describe the methodology of activities undertaken, which were functional to clearly answer each research question moving the goals of the study itself, as depicted in the following figure.

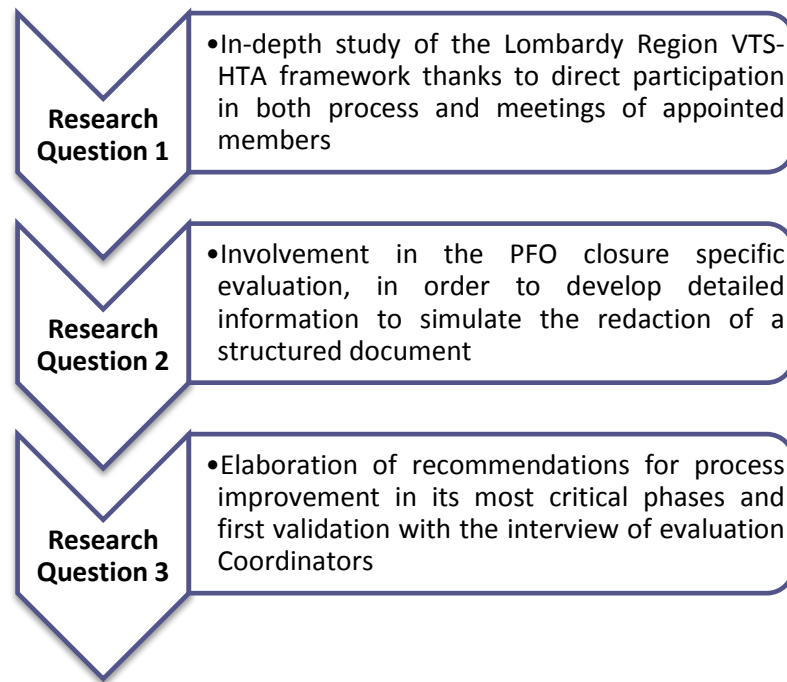


Figure 3.1 - Flow chart of the activities performed

3.1 Meetings and Direct Participation to the VTS-HTA Process

In order to answer to the **“RQ1: Is current architecture of the VTS-HTA model properly legitimized?”**, the opportunity to take direct part on the Lombardy Region process for Technology Assessment, namely VTS-HTA (in Italian, Valutazione delle Tecnologie Sanitarie – Health Technology Assessment) enabled a in-depth understanding of how theory could be put into practice, and which is the proper sequence of activities to be performed and the related complexity of each one of them. Furthermore, the literature analysis and the emerged gaps prepared a secure ground for legitimizing the “modus operandi” which is currently adopted.

The first step consisted in the theoretical verification of the design of the VTS-HTA framework: as it was presented, the procedure is defined according to the NICE approach, i.e. with the distinct phases of Scoping (here called “Prioritization”), Assessment and Appraisal. Thereafter, the single evaluation elements are incorporated and tailored from the EUnetHTA and EVIDEM frameworks: in fact, assessment topics and issues are provided by EUnetHTA Core Model, while the procedure for

decision making is supported by the Multi-Criteria Decision Analysis technique from the EVIDEM Collaboration. Thus, the process of integration of these two different models into the VTS-HTA one introduced some operational changes, in order to cope with the specific context of application: in particular, high-level dimensions are consistent with the EUnetHTA domains, EVIDEM-based criteria are redefined and embedded into the EUnetHTA framework, and, finally, the correspondence between issues and topics and between topics and domains has been properly redefined.

The second step consisted in many face-to-face meetings, which were planned with the General Healthcare Directorate (i.e. the leading body for government of territorial health services and policies for appropriateness and control) representatives, who directly explained the three macro-phases of the process, i.e. Prioritization, Assessment and Appraisal, and then the single activities in which participants are involved. In each phase, actors with different roles are enrolled, in order to provide complementary contribution to the overall decision making system: as it will be further described in next chapters, two groups of professionals coming from different scientific backgrounds are permanent for the beginning and the conclusion phases of the process, while during the central step a panel of experts on the specific technology of interest is created in order to provide peculiar information for editing robust documentation for the evaluation itself. Thus, personal participation was also possible at meetings of both permanent groups and experts' panel, in order to better understand their level of involvement knowledge of how the process works, and to try to identify what could be particular difficulties emerging during discussions. In fact, meetings were planned with twofold objective: on the one hand, they were important for the General Healthcare Directorate to show the level of progress of the evaluation itself, while, on the other hand, participants were encouraged to directly share their possible doubts in order to further analyze available opinions and proceed to the next step of the process. Moreover, as meetings are planned monthly for each independent group of participants, a specific tool for remote interaction between General Healthcare Directorate and other actors has been created, i.e. the internet portal www.mappabiomedicina.it, as it will be further explained in the next chapter.

This close study was, hence, important in order to better focus on how activities and sub-tasks of the VTS-HTA framework were designed, and to reflect on their related targets for architecture legitimization.

3.2 Contribution to the PFO Closure Evaluation and Simulation

After a first presentation of the workflow of activities, the involvement in a specific technology evaluation was established to focus, this time, on the peculiar model which is used for priority setting and to answer the **“RQ2: Is the current process efficient in order to guarantee a straightforward**

and transparent functioning from the perspectives of exchanges of information and organizational structure?”. In fact, the previous activity resulted to be functional, in this perspective, to better understand how documentations are structured and elaborated to support effective decision making and how actors are involved to efficiently combine their knowledge for process advancement. The case of the procedure for Patent Foramen Ovale (PFO) closure, an intervention to repair a heart defect which is aimed at treating recurrent stroke and migraine, was presented and followed from its early Prioritization stage to the Assessment, which is the point currently achieved.

Direct participation to the meeting of the Assessment experts' panel was then useful to understand which are the typologies of competences needed for a thorough clinical investigation of available evidence on the topic of interest, and how it is arranged in order to provide best utility to the following Appraisal step, which is aimed at evaluating the documentation collected and judging the appropriateness of use of the technology itself.

In this specific situation, it was possible to establish, on the one hand, the main determinants of the algorithm used for decision making, i.e. the Multi-Criteria Decision Analysis (MCDA), and, on the other hand, the level of confidence at which the General Healthcare Directorate uses the model itself. Furthermore, from a detached perspective, upsides and downsides of the process became more evident, even more during the phase of release of the ad hoc forum on the internet portal, which was aimed at creating a base for knowledge and experience sharing. At this point, tasks were subdivided among different experts, and Coordinators for the evaluation were appointed in order to determine process owners who could encourage direct participation and moderate discussions on the forum. A collaboration was started with Age.Na.S., the National Agency for Regional Health Services, to develop a rapid HTA with a systematic review of literature, moreover the analysis of the regional Data Warehouse was commissioned by the General Healthcare Directorate in order to corroborate literature results with contextual information.

Separately from the VTS-HTA process, it was then decided to simulate the Assessment process of redaction of a structured multi-criteria report, namely the SIM (Stima di Impatto Multidimensionale – Multidimensional Impact Estimate), which is a document, as it will be further explained later, where evidence collected from literature, with additions provided by experts, is stratified according to the different criteria of the MCDA model. This segmentation will be functional to the following judgment of the Appraisal committee, which will allocate weights and scores to determine the MCDA Index, an indicator to support final discussion for appropriateness of use of the technology.

Thanks to the supervision of one of the four Coordinators of the PFO evaluation, a literature search was undertaken and resulting articles were then clustered according to the disease and the typology

of study. Afterwards, sources were analyzed and information was separated in relation to different criteria and issues. During the study, this relevant step was valuable to directly face real problems which panelists meet in their task, thus a thorough reflection on purpose and meaning of each component enabled questions to be solved in order to improve the overall process. Moreover, direct involvement into the procedure made easier a straightforward contact with implicated personnel and a first-hand experience of what are the main forces in play and the possible related drawbacks, which occur by nature as procedures follow their first implementation.

3.3 Recommendations

The analysis of the VTS-HTA framework led to the **“RQ3: What are the main levers driving an effective improvement of both design and management structure of the process?”**, and to the subsequent contemplation of each single component characterizing two main pillars which were identified: on the one hand the decision making model, which has been embraced by incorporating and contextualizing other international examples, and, on the other hand, the organizational structure, which both affects and is affected by how the process itself is designed. These driving reasons moved towards the elaboration of unsolved questions and issues which could be still answered, and a deepened rethinking about what were the main inconsistencies and gaps to be overcome.

Thus, the observation of the process was not an end in itself, since, instead, many argumentations arose from the necessity of making leaner and more effective the as-is complex system. Thanks to brainstorming and consultation of results from a questionnaire previously submitted to VTS-HTA members, further explanations of why problems had consistence and how they could be solved were then followed by the formulation of appropriate recommendations for both the decision model's and the organizational structure's issues, which should induce an improvement on how the process is perceived by its main users. By discussing its main features, it was possible to focus on levers driving the achievement of the final goal, i.e. the decision of appropriateness of use for the technology; furthermore, the proper involvement and engagement of key stakeholders was found to be an essential pillar and motivator for the procedure itself, as it effectively works upon a specific understanding of roles, different aspects and components of the decision model, and documentation exchanges.

In the end, feedback from the General Healthcare Directorate and a reflection about possible decision making impacts on core dimensions of the system itself, which lead to interviews to the Deputy Director of the HTA Program and to the four Coordinators of the PFO evaluation, were attached for validation of the research developed, strengthening the necessity of always contextualizing theories, but also requiring field testing and constructive comparison.

4. VTS-HTA in Lombardy Region

4.1 Italian Network for HTA

The holistic approach of HTA is applied at different levels of the healthcare system in order to encourage, involve and give a sense of responsibility to decision makers around methodologies, tools and rationalization actions of the decision making process itself. Although in other European and international countries the HTA process was already established from many years, in Italy the principles of HTA were implemented only in 2006, with the “Carta di Trento” (see Annex C), after a reflection of the Italian Network of Health Technology Assessment (Italian acronym NI-HTA), a body established in 2003 thanks to a project funded by the Italian Ministry of Health (Ricciardi, et al., 2010). This document regarding the evaluation of healthcare technologies is aimed at identifying all the main values which move the rationale of enhancing the healthcare system, the proper management choices at national, facility and each level of clinicians’ practice, the involvement of stakeholders by supporting the multidisciplinary approach and respecting principles of equity and transparency (NI-HTA, 2006).

The NI-HTA brings together some Italian companies which matured expertise on HTA within a interorganizational collaboration, in order to promote the standardization of a technology evaluation model supporting managerial decisions, which can be exported to the National Health Service (Servizio Sanitario Nazionale – SSN), and to foster knowledge sharing among managers and health workers. Thus, Italy represents the only exemplification at international level embracing HTA first at organizational level (companies) and just later at higher level (regional or national).

The regional perspective is noticeably diversified, as in two regions only, Emilia Romagna and Veneto, a long experience has been developed in priority definition, research, evaluation and diffusion of knowledge regarding healthcare technologies, which provides a support to health policy decisions; other regions, such as Lombardy, Piemonte, and Tuscany deliberated the starting phase of programs integrating HTA principles and methods within the regional decision processes. Furthermore, a model such as the Spanish one, where the single regions develop assessment activities under a national coordination which harmonizes systems and avoids duplications of processes throughout the different environments, could enable the single regional agencies to specialize in a certain field of evaluation: drugs, diagnostic tests, medical devices, etc. (Cicchetti, 2008). Lacking a proper national agency which is deputed to the leadership of HTA evaluations and to the systematization of the related activities, a first role has been assumed by the National Agency for Regional Health Services (Agenzia Nazionale per i Servizi Sanitari Regionali – Age.Na.S.), by promoting the collaboration and

coordination for the systematic assessment of healthcare technologies at regional level (Rete Italiana di HTA – RIHTA) and the activities of Horizon Scanning (HS), which detect the possible impacts of emergent technologies on the SSN.

Overall, although the 71,4% of the Italian regions recognized HTA activities as future priorities, by adding them in each Regional Health Plan (Piano Sanitario Regionale – PSR), only the 47,6% of them arranged a formal regulation: Lombardy, Tuscany and Veneto regions (14,3%) planned a dedicated budget for these activities and Emilia Romagna and Veneto regions a funding program aimed at healthcare technology value judgment. Thus, the need for investing in a proper training system is clear, with the primary goal of monitoring professional skills and outcomes achieved in every particular area. This could enable the network to share both knowledge and results, hence optimizing resources and investments (Ricciardi, et al., 2010).

The next paragraphs will explain how and why the Lombardy Region differentiates itself from other regional organizations, showing the background of development of the present study.

4.2 Lombardy Region: Contextualization and Model

The Lombardy Region healthcare system serves 9,9 million inhabitants through 15 local health agencies, 34 public hospitals and other 200 healthcare organizations, being considered the leading healthcare system in Italy thanks to its capabilities of delivering state-of-art care and healthcare expenditure containment. In fact, this system is one of the few regional healthcare systems in Italy showing balance between cash inflows and cash outflows, while other systems collected relevant deficit during the years and the Ministry of Health was obliged to strictly monitor and reduce their autonomy in resource utilization (Luzzi, et al., 2012).

The adoption of new healthcare technologies entails dealing with uncertainty, risk and complexity of processes; thus, the Lombardy Region became aware that a proper development towards sustainable effectiveness and appropriate decision making in the current economic situation couldn't be successful without:

- The consolidation of *legitimized* practices for assessing the healthcare programs and technologies and selecting the higher “value for money”;
- The *leverage* on distributed *individual knowledge* that belongs to professionals – physicians, engineers, economists, lawyers, etc. – who contribute with their daily practice to both the delivery of care (i.e. practitioners) or the advancement of knowledge in healthcare (i.e. academicians);

- The constitution of formal *benchmarking activities* with leading international and national agencies.

Legitimization by key stakeholders (i.e. healthcare providers, patient groups, technology suppliers) is gained when the decision making exercise is respectful of their views and complying their perception of what is appropriate. Hence, the three most important requirements for decision making, identified by the Lombardy Region, are rationality, fairness and efficiency. The first issue refers to the adoption of proper decision models, formalizing all the results obtained in specific documents afterwards, while the second one is related to the adoption of the “accountability for reasonableness” (A4R) framework which provides the pragmatic background for promoting relevant stakeholders’ agreement. Efficiency can be achieved thanks to the endorsement of methods guaranteeing timely and cost contained decision making.

The challenge of learning and improving stems from the necessity of “going beyond the information systems” by implementing different internal mechanisms and organizational roles which can effectively shape experts’ knowledge sharing behavior. Furthermore, it’s important to reach a balance between organizational theoretic models and actual engagement of the community of decision makers, as achieving their maximum level of active participation often reveals to be a barrier.

The benchmarking from and with leading HTA agencies is relevant as a prerequisite for promoting collaborations and being always updated, thus joining international organizations and building a formal relationship with Age.Na.S. and RIHTA network enabled the Lombardy Region to both assimilate new approaches and information, and make available to other regions the practices developed.

The program named “Valutazione delle Tecnologie Sanitarie – Health Technology Assessment” (VTS-HTA) was launched with the regional deliberation DGR n. 8/7856 of July,30th 2008 (see Annex D) and applied with the two decrees of the General Healthcare Directorate (Direzione Generale Sanità) DDG n. 11858/2009 and n. 14013/2009, with the aim of depicting the whole post-license evaluation course of healthcare technologies and their impacts (clinical, economic and social) on the current market, and providing information to both improve patients’ access to treatments and prevent inappropriate and wasteful diffusion of practices.

The VTS-HTA framework thus incorporates and adapts elements from the EUnetHTA and the EVIDEM frameworks: in fact, on the one hand dimensions, topics and issues are provided by EUnetHTA Core Model, and on the other hand decision making is supported by the Multi-Criteria Decision Analysis

technique from the EVIDEM Collaboration. The procedure has been introduced at macro-level, and three elements have been standardized:

1. The VTS-HTA *process*, i.e. the defined phases to (a) acquire and prioritize requests of healthcare technology assessment, (b) perform a multidimensional and evidence-based assessment of the technologies themselves, and (c) appraise the results;
2. The VTS-HTA *actors*, i.e. (a) the NVP-CI (Nucleo di Valutazione Priorità e Conflitti di Interesse – Unit of Prioritization and Conflict of Interests) responsible for the prioritization, (b) the group of experts, who are identified on the purpose of a specific evaluation, and (c) the TTRAM (Tavolo Tecnico Regionale per l'Appropriatezza in Medicina – Regional Technical Roundtable for Medical Appropriateness) responsible for the appraisal of technologies;
3. The VTS-HTA *model*, i.e. the knowledge base adopted for the multidimensional and evidence-based assessment.

Thus, the process of integration between the different models introduced some operational changes within EUnetHTA and EVIDEM models, in order to best cope with the specific context of application, and in particular it:

- a. Defined high-level dimensions consistent with EUnetHTA domains;
- b. Redefined EVIDEM criteria to best show their applicability;
- c. Embedded EVIDEM-based criteria into EUnetHTA framework;
- d. Redefined the correspondence between issues and topics and between topics and domains.

Furthermore, the VTS framework endorses a cost-opportunity approach, in order to adapt the analyses to the context issues: new technologies are appraised by their capacity to substitute obsolete ones or to improve the care pathway, thus implementing a zero-sum logic of balance between adoption and delisting. EUnetHTA domains are mapped into dimensions that the Lombardy Region sets up to legitimize the prioritization of technologies, then criteria from the EVIDEM open source framework are included to best support the systematic appraisal of the assessment report into a final decision. Both “dimensions” and “criteria” are consistent with the Core Model as they do not distort its logic, structure and contents (Radaelli, et al., Working paper).

The three main elements previously defined will then be further described backwards, in order to first determine the tools which compose the implemented *model* and then the *actors* and the purpose itself to which the HTA *process* in Lombardy Region is addressed.

As firstly identified in the regional deliberation, the dimensions of evaluation for healthcare technologies are eight, and can be easily compared to domains of the EUnetHTA Core Model, as shown in the table below:

VTS	EUnetHTA Core Model
Dimension	Domain
1. General Relevance	1. Health problem and current use of technology 2. Technical characteristics of technology
2. Safety	3. Safety
3. Efficacy (Clinical research)	4. Clinical effectiveness
4. Effectiveness (Practical medicine)	
5. Economic and financial impacts	5. Cost and economic evaluation
6. Equity	6. Ethical analysis
7. Social/ethical impacts	7. Social aspects
8. Organizational impacts	8. Organizational aspects 9. Legal analysis

Table 4.1 - Comparison between VTS dimensions and EUnetHTA domains

More specifically, the dimension “Effectiveness” is careful in particular to chronic pathologies and complex subpopulations with high levels of co-morbidities (i.e. concomitance of two distinct diseases), while Equity refers, for instance, to the impact of a mix of diagnostic-therapeutic technologies induced by the adoption of a innovative technology. The “Social/ethical impacts” concern qualitative analyses of satisfaction or acceptability which are not immediately clear as implications deriving from the use of technologies, while the “Organizational impacts” regard the implementation and maintenance of certain technologies (DGR Regione Lombardia, 2008).

Since the Core Model provided only a detailed and standardized procedure for data collection, and didn’t suggest explicit tools or techniques for the appraisal of evidence, at this point the VTS framework adopted the criteria developed by EVIDEM which thoroughly took into consideration strengths and weaknesses of the technology itself. VTS counts on 21 criteria, which often are the literal translation of the EVIDEM ones, while minor changes include, for instance, three EVIDEM criteria (related to Quality of evidence) incorporated into two criteria (Completeness and consistency of documentation, Relevance and validity of documentation) to be consistent with VTS procedure of data collection; the extension of the EVIDEM “Political/Historical Context” into VTS criterion “Coherence with National and Regional Planning”. These changes don’t jeopardize the principles of completeness, non-redundancy and independence.

The comparison between the VTS framework and the EVIDEM criteria are described in the following table:

VTS	EVIDEM
General Relevance D1 Description and severity of illness C3 Size of population C4 General Healthcare Goals C5 Description of technology and benefits areas C6 Completeness and consistency of documentation C1 Relevance and validity of documentation C2	D. Disease impact Disease severity Size of population T. Type of benefit Public health interest Type of medical service Q. Quality of evidence Adherence to decision making body Completeness of reporting evidence Relevance and validity of evidence
Safety D2 Improvement of Safety and Tolerability C7 Efficacy and Effectiveness D3, D4 Improvement of Efficacy and Effectiveness C8 Improvement of patient related outcomes C9 Guidelines & good practice recommendations C10 Limitations of alternative technologies in use C11	I. Intervention outcomes Improvement of efficacy/ effectiveness Improvement of safety & tolerability Improvement of patient reported outcomes C. Context of intervention Clinical guidelines Comparative interventions limitations
Economic and Financial Impact D5 Financial Impact on Health system C12 Cost-effectiveness C13 Impact on other spending C14 Impact on efficiency (cost-opportunity) C15*	E. Economics Budget impact on health plan Cost-effectiveness of intervention Impact on other spending
Equity D6 Impact on equity and accessibility C16* Social and Ethical Impact D7 Coherence with national, regional planning C17 Impact on healthcare needs C18* Pressure of interest groups C19* Historical and political context C20* Organizational Impact D8 System capacity, appropriate technology use C21*	Et. Ethical framework Goals of healthcare – utility Opportunity costs – efficiency Population priority & access – fairness O. Other criteria System capacity & appropriate use of intervention Stakeholder pressures Political/historical context

Table 4.2 - Comparison between VTS dimensions (D) and criteria (C) and EVIDEM criteria (* indicates implicit criteria)

Such as EVIDEM extrinsic criteria, 15 VTS criteria are defined as computable, since they are referred to properties which can be measured. The other remaining six criteria are considered intrinsic because it is questionable to refer them to specific measurable properties and their evaluation is strictly connected to an overall judgment of the specific context. These criteria are:

- Impact on efficiency (cost-opportunity)
- Impact on equity and accessibility
- Impact on healthcare needs
- Pressure of interest groups
- Historical and political context
- System capacity, appropriate technology use

Moreover, at a further level of detail, the EUnetHTA topics and issues are retrieved to actively operationalize each VTS criteria.

In conclusion, the operationalization of the Core Model occurs through an explicit and full adoption of its issues and topics, fundamental for data collection and the assessment of technology impacts and the inclusion of EVIDEM criteria for the MCDA, fundamental, instead, for the appraisal of requests. The integration between EUnetHTA and EVIDEM is unproblematic, as the former provides elements for collecting data and assessing impacts while the latter the instruments for clarifying and making actual decisions (Radaelli, et al., Working paper); thus the two methods can be implemented without compromising their respective objectives and approaches, assuring rigorous and transparent decision making.

4.3 VTS-HTA Actors

As previously mentioned, different roles with different functions take part in the decision making process throughout the VTS system. First, the General Healthcare Directorate is charged of planning and technically controlling the health policies under evaluation. A technical contribution to the General Healthcare Directorate is also provided by a group of professionals who operate in two evaluation bodies, the Unit of Prioritization and Conflict of Interests (Nucleo di Valutazione Priorità e Conflitti di Interesse – NVP-CI) and the Regional Technical Roundtable for Medical Appropriateness (Tavolo Tecnico Regionale per l'Appropriatezza in Medicina – TTRAM).

The NVP-CI group is elected for three years and it is composed by 18 regular members and 18 substitutes coming from Local Health Authorities, foundations, associations and faculties appointed by the Region itself. One or more than one components of the NVP-CI has also the role of Coordinators of the assessment project and supports the General Healthcare Directorate in some activities regarding the priority judgment and the first draft of the final documentation regarding the SIM (Stima di Impatto Multidimensionale - Multidimensional Impact Estimate), as it will be further explained later.

In the next table the NVP-CI components are listed in alphabetic order: empty spaces refer to those members who have been appointed but lately changed his/her reference organization and were then resigned. It's important to note that, as the first program ended last October, 31st 2012, the new commission of elected components (currently under development) can be subjected to changes and will be effectual for the next three years.

Name			Representative organization
	Regular	Substitute	
1	Pietro Aronica	Sandrina Masiello	A.S.L. di Brescia
2	Pietro Barbieri	Cristina Papetti	A.O. di Melegnano
3	-	Paolo Lago	Fondazione IRCSS Policlinico San Matteo di Pavia
4	Luca Cavalieri D'Oro	Cambiaghi Tarcisio	A.S.L. di Monza-Brianza
5	-	Francesco Bertolini	Istituto Europeo di Oncologia S.r.l. Milano
6	Francesco Di Meco	-	Fondazione IRCSS Istituto Nazionale Neurologico Carlo Besta
7	Stefano Giulini	Arianna Coniglio	A.O. Spedali Civili di Brescia
8	Loredana Luzzi	-	A.O. Garbagnate Milanese - A.O. G. Salvini
9	Patrizio Piacentini	Elisabetta Camarchio	A.O. Ospedale San Carlo Borromeo
10	Camillo Rossi	Catia Barosi	A.O. Istituti Ospedalieri Cremona
11	-	Emanuele Bosi	Fondazione IRCSS Centro S. Raffaele del Monte Tabor, Milano
12	Silvana Castaldi	Paolo Cassoli	Fondazione IRCSS "Ospedale maggiore Policlinico. Mangiagalli e Regina Elena", Milano
13	Maria Rosa Dellagiovanna	Carlo Cerra	A.S.L. Pavia
14	Mauro Agnello	Emérico Panciroli	Ospedale Sacco
15	Claudio Rossetti	Salvatore Siena	A.O. Ospedale Niguarda Ca' Granda
16	Marco Villa	Alfredo Cocci	A.S.L. Cremona
17	Olivia Leoni	Rulli Giovanni	A.S.L. Varese
18	Paolo Casali	Vincenzo Bombardieri	Fondazione IRCCS Istituto Nazionale per lo studio e la cura dei tumori di Milano

Table 4.3 - Members of the NVP-CI

The TTRAM is a group aimed at evaluating the appropriateness of healthcare technologies according to the Regional Health Service (Servizio Sanitario Regionale – SSR) perspective and is composed by 69 members coming from Local Health Authorities, foundations, faculties and private Health associations, pathology networks and regional commissions, who are selected and appointed by the Region with variable length. The TTRAM is divided in four equipotent subgroups (A, B, C, D) for specific assessments, and the assignment of which appropriateness evaluation each subgroup should undertake has been randomly decided for the first time in 2010, then in February 2011 and the last on January, 26th 2012. Moreover, as for the NVP-CI, one or more than one components of the TTRAM, not involved in the subgroup which assigns weights and scores for the appropriateness decision, have the role of Coordinators of the assessment and supports the General Healthcare Directorate mainly during the assessment phase.

The TTRAM members and their subgroups are listed in the following table:

	Name		Representative organization
TTRAM (Group A)	1	Valter Valsecchi	A.S.L. Lecco
	2	Ivo Bergamo	A.O. Ospedale Civile di Legnano
	3	Maurizio Morlotti	A.O. Ospedale di Lecco
	4	Oscar Di Marino	A.O.S. Gerardo dei Tintori, Monza
	5	Salvatore Chiarella	Policlinico San Donato S.P.A.
	6	Tiziano Lucchi	IRCCS Policlinico Ca' Granda Milano
	7	Maurizio Castellano	Università Statale di Brescia
	8	Silvio Garattini	Istituto Mario Negri
	9	Davide Croce	Università Cattaneo, Liuc, Crems
	10	Stefano Perlini	Ordini Medici - FROMCeO
	11	Giuseppe Micieli	Commissione Regionale Cerebro cardiovascolare
	12	Paolo Ravelli	A.O. Bolognini Seriate
	13	Laura Gorini	A.O. Ospedale di Circolo Fondazione Macchi, Varese
	14	Vincenzo De Cristofaro	A.O Valtellina e Valchiavenna
	15	Lisa Licitra	Rete Oncologica Lombardia
	16	Maurizio Marzegalli	Commissione Regionale Cerebro cardiovascolare, Rete Cardiologica
	17	Stefano Capri	Università Cattaneo, Liuc, Economia
TTRAM (Group B)	1	Giuliana Sabatino	A.S.L. di Como
	2	Massimo Medaglia	A.O. Sacco
	3	Cesare Verdoia	Istituto Ortopedico G Pini, Milano
	4	Mario Lanfredini	A.O. S. Paolo, Milano
	5	Lorenzo Cammelli	Centro Cardiologico S.P.A. Fondazione Monzino, Milano
	6	Giorgio Tarassi	Ordine dei Camilliani, Provincia Lombardo-Veneta
	7	Gianmario Frigo	Università Statale di Pavia, Medicina
	8	Elena Tremoli	Università Statale di Milano, Farmacia
	9	Giovanni Belloni	Ordini Medici - FROMCeO
	10	Giuseppe Enrico Rivolta	Ordini Medici - FROMCeO
	11	Gedeone Baraldo	Rete delle malattie rare
	12	Alberto Onetti	Università dell'Insubria – Facoltà di Economia
	13	Giovanni Meroni	A.O. Treviglio
	14	Roberto Labianca	Rete Oncologica Lombardia
	15	Stefano Cipolla	IRCCS Casa di cura multimedica - Holding Spa
	16	Francesco Pincioli	Università Politecnico di Milano, Ingegneria Biomedica
	17	Pierluigi Guidali	A.O.S. Antonio Abate di Gallarate
	18	Giorgio Annoni	Università Statale di Milano Bicocca, Medicina
TTRAM (Group C)	1	Maurizio Galavotti	A.S.L. di Mantova
	2	Giorgio Barbaglio	A.O. Desenzano del Garda
	3	Antonio Piccichè	A.O. Spedali Riuniti Di Bergamo
	4	Franco Vimercati	A.O. Fatebenefratelli e Oftalmico - Macedonio Melloni, Milano
	5	Massimo Molteni	IRCCS Istituto Eugenio Medea - Associazione La Nostra Famiglia

	6	Emanuele Lettieri	Università Politecnico di Milano, Ingegneria Gestionale
	7	Silvano Cella	Università Statale di Milano, Medicina
	8	Andrea Mandelli	Ordini Farmacisti
	9	Marco Stramba-Badiale	Istituto Auxologico Italiano
	10	Marco Cambielli	Ordini Medici - FROMCeO
	11	Norberto Silvestri	IRCCS Humanitas Mirasole S.P.A., Rozzano
	12	Giovanbattista Ippoliti	A.O. Pavia
	13	Annamaria Indelicato	A.O. Mellino Mellini
	14	Maurizio Maccarini	Università Statale di Pavia, Economia
	15	Francesca Kainich	Università statale di Milano Bicocca, Economia
	16	Gianfrancesco Fiorini	A.O. Ospedale Maggiore di Crema
	17	Americo Cicchetti	Università Cattolica del Sacro Cuore, Cerismas
TTRAM (Group D)	1	Giancarlo Sportelli	A.S.L. di Lodi
	2	Alberto Martegani	A.O. S. Anna di Como
	3	Lucio Attolini	A.O. "C. Poma" di Mantova
	4	Franco Pavesi	A.O. Lodi
	5	Enrico Eugenio Guffanti	IRCCS Istituto I.N.R.C.A., Casatenovo
	6	Giovanni Fattore	Università Commerciale L. Bocconi, Cergas
	7	Angelo Buizza	Università statale di Pavia, Dpt Informatica e sistemistica
	8	Aurelio Sessa	Ordini Medici - FROMCeO
	9	Giovanni Gerosa	Ordini Farmacisti
	10	Salvatore Siena	Rete Oncologica Lombardia
	11	Giuseppe Banfi	Istituto ortopedico Galeazzi S.P.A., Milano
	12	Jorge Salerno Uriarte	Comm. CCV - Bioimmagini
	13	Gabriele Caccialanza	Università Statale di Pavia, Farmacia
	14	Francesco Triscari Binoni	A.O. Desio e Vimercate
	15	Mauro Ricca	Fondazione Don Carlo Gnocchi Onlus
	16	Luigi Beretta	Università Vita e Salute - San Raffaele, Medicina
	17	Paola Pirola	Istituti clinici di perfezionamento, Milano

Table 4.4 - Members of the TTRAM

Besides the NVP-CI and TTRAM members, who are permanent, the General Healthcare Directorate is assisted in its decisions by a Workgroup (Gruppo di Lavoro – GdL) of qualified experts, who are chosen by the Coordinators as specific witnesses of a scientific domain coming from different backgrounds, professional organizations and scientific schools. Thus, these experts, chosen ad hoc for each evaluation, upon an assessment of possible conflicts of interest, provide individually their contribution, but the final assessment document reports the signature of all the participants in a shared view. However, the ultimate goal of the panel of experts is not the definition of a professional consensus, but the acknowledgement of the technology properties examined both in the specific research context and in the usual practice. In fact, the presence of different perspectives in the final report, as long as legitimate, is considered to be appropriate, since experts are not assigned for the

decision of appropriateness of the technology under consideration. The TTRAM is set for this purpose and, ultimately, this will be the General Healthcare Directorate's competence.

Throughout the next paragraph the single phases of the VTS-HTA process will be deepened in detail, referring to its three main steps: prioritization of requests, assessment of the evidence about the technologies, and appraisal of results, as clearly depicted in the summarizing figure below (Radaelli, et al., Working paper).

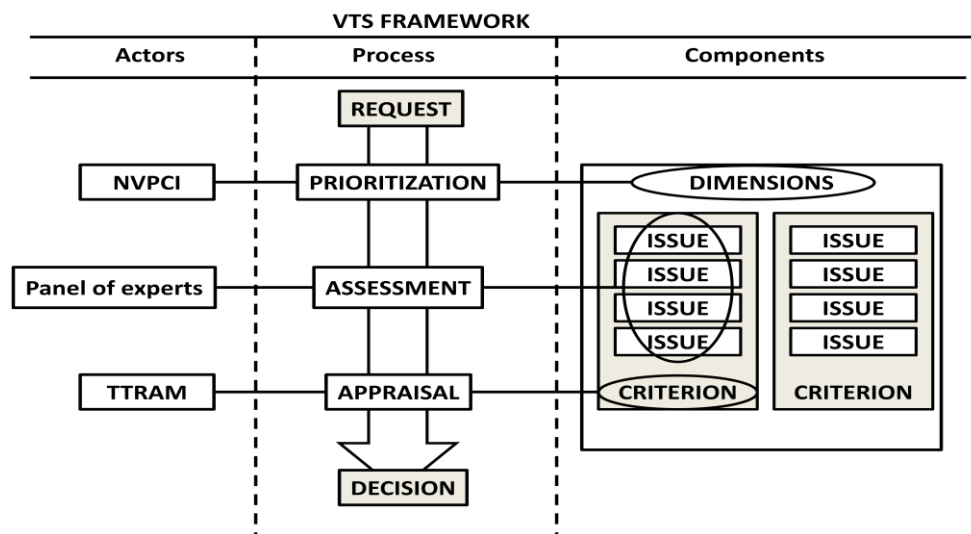


Figure 4.1 - Actors, process and components of the VTS framework

4.4 VTS-HTA Process

The VTS-HTA is a knowledge management process aimed at providing decision makers with safe, effective, patient- and best health value-oriented regulations at all the different levels of the SSR, and investigating different impact dimensions of healthcare technologies by comparing their benefits and costs. Thus the three macro-processes, which have been previously mentioned, are (OECD, 2005):

- 1) Identification of priorities and necessity of evaluations throughout the healthcare system;
- 2) Systematic retrieval and analysis of efficacy and effectiveness documentations, or explicit declaration of their lack;
- 3) Critical evaluation and appraisal of available documentations, including the judgment of the practical meaning (application) of the technology itself in the healthcare system perspective.

The specific objectives within the evaluation process, which have to be clear throughout each phase, are:

- a) Manage the level of uncertainty of information (sometimes unavoidable);
- b) Manage the transferability of evaluations developed in other national and international contexts into the Regional Healthcare System (including research results);

- c) Test innovative approaches throughout the practical use of biotechnologies, biomedicines, biosimilars, and cutting-edge products and processes in general;
- d) Manage the former issues into a decision model oriented towards both the economic sustainability and the specific interventional appropriateness in the Regional healthcare context.

4.4.1 Prioritization

The first phase of the VTS-HTA process is undertaken by the NVP-CI, which determines the degree of priority of each healthcare technology under evaluation.

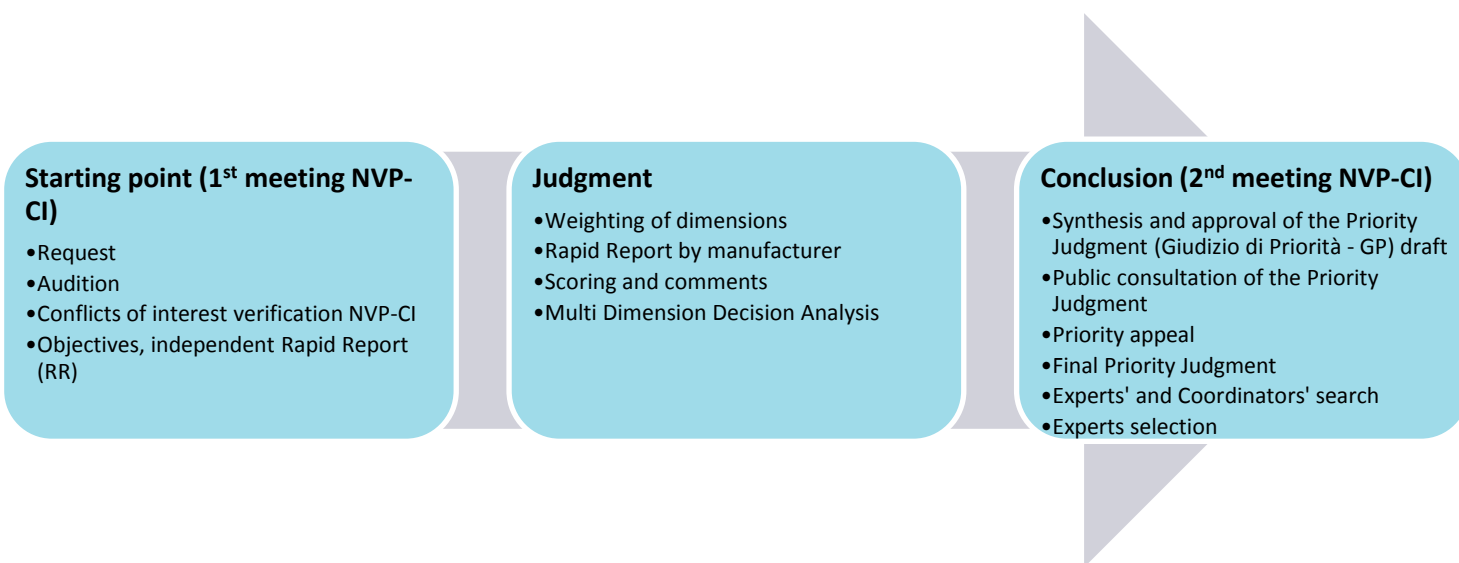


Figure 4.2 - Example of Prioritization workflow

Starting point

The Lombardy Region receives every year a large amount of requests proposing the introduction of new technologies, or indicating the inappropriate use of them, through both formal and informal channels, from different stakeholders (healthcare organizations, private manufacturers, professional societies, patients associations). Since performing a full assessment for every technology is unfeasible, the Regional deliberation n. 8/7856 (DGR Regione Lombardia, 2008) delineates a standard procedure that formalizes which technologies can access assessments and how the priority decision must be made. Requests can originate only from “accredited actors”, ranging from no-profit (i.e. care-giving organizations included in the Regional Health Database, scientific and professional societies, patients associations and universities) to for-profit organizations (i.e. pharmaceutical, biotech, diagnostic firms). Technologies under evaluation are: drugs, medical devices, diagnostic tools, screening procedures, diagnostic-therapeutic and rehabilitative pathways, organizational and support systems (information, training and administrative) which can change the appropriate use of technologies. All requests must attach a documentation that indicates: (1) general features of the

proposed technologies, (2) technological mix which is going to be substituted, (3) key evidence that describes the impacts of the technology. Incomplete documentation is a sufficient condition for desk-rejection of requests (Radaelli, et al., Working paper).

At the request phase, the components of the NVP-CI fill in a specific absence of conflicts of interest agreement for the technology through a downloadable form on the internet portal www.mappabiomedicina.it, section “Priorità” of the technology under evaluation. This portal is progressively giving way to the new one, www.mappabiomedicina1.it/hta, which, even though still a “beta-version” and edited only for some devices and drugs, has more interactive and communication tools thanks to which users can submit their contributions, such as spaces for comments and a forum with topics and threads available for each step of the assessment.

The request of evaluation is discussed during the NVP-CI meeting, after a 30 minutes audition of the applicant company. During the following weeks, the Coordinator(s), who are appointed for the technology by the NVP-CI, cooperate with the General Healthcare Directorate in the editing of a Rapid Report (Rapporto Sintetico – RS), which summarizes benefits and issues connected to the use of the technology, according to the eight VTS dimensions (cf. Table 4.1). This document helps the components of the Unit to express a Priority Judgment (Giudizio di Priorità - GP), that has to be completed usually in two weeks.

Priority Judgment

After receiving the documentation, each component of the NVP-CI indicates the relative importance of every dimension by assigning anticipatory weights from 1, higher relevance, to 8, lower relevance, thus ranking the dimensions according to a preference order. Afterwards, scores and comments are collected for each dimension regarding the personal opinion of each member about the meaning of the technology for the SSR. Scores reflect how the technology under evaluation performs compared with other competitor ones and can be assigned in a discrete scale from 0 to 4 meaning:

- 0 = when no reliable or sufficient information is available to evaluate the technology (this mostly happens in case of technologies of recent introduction into the market or in case of lack of robust scientific documentation)
- 1 = lower performance
- 2 = comparable performance
- 3 = performance marginally higher
- 4 = much higher performance

When all the Priority Judgments are collected, the Multi-Dimension Decision Analysis (which is the same as the Multi-Criteria Decision Analysis – MCDA, but during this phase VTS dimensions, and not yet VTS criteria, are assessed) is implemented in order to:

1. **Calculate the Priority Index for the SSR:** the index is calculated thanks to a linear additive model as follows; comments to the result are provided by the General Healthcare Directorate and the NVP-CI Coordinators of the evaluation.

$$\text{Rank}(\text{technology } j) = \sum_{i=1}^8 [\text{weight}(\text{dimension } i) \times \text{score}(\text{dimension } i, \text{technology } j)]$$

2. **Facilitate the qualitative analysis of comments:** the evaluation Coordinators examine comments and resolve possible disagreements by conversation or participation of another member.

Conclusion

The NVP-CI Coordinators, in cooperation with the General Healthcare Directorate, edit a Priority Judgment (Giudizio di Priorità – GP) draft with an overall evaluation which will be submitted to the whole NVP-CI panel, who will have the task of verifying and approving the documentation related to the final decision of acceptability of the technology to the full assessment. The GP can have three results:

- a. Rejection (assessment request not accepted);
- b. Request accepted upon further documentation provided;
- c. Request accepted with a certain priority degree:
 - C1, if the technology is of high interest for the system; in this case, 4 months are necessary to conclude the assessment;
 - C2, if the technology is of moderate interest for the system; in this case, 8 months are necessary to conclude the assessment;
 - C3, if the technology is of low interest for the system; in this case, 12 months maximum are necessary to conclude the assessment.

Afterwards, a summary of both documentation and reasons for the decision are published on the internet portal for two weeks, so that further comments or proposals of integration can be submitted by competitor companies, professionals, patients and citizens; when the result of the Priority Judgment is negative, a request for appeal can be put forward by the company itself and a further audition can be performed. After the audition, the General Healthcare Directorate will

confirm the previous result or the acceptance of the assessment request; in this latter case, the next step will be the assessment phase.

Prior to this step, however, domain experts are identified for the evaluation, and manufacturers, as well as citizens and patients associations, are enabled to provide further scientific documentation for consultation through the suited form on the new internet portal -> section “Condivisioni”.

4.4.2 Assessment

The assessment is a technical verification of the technology according to the impact dimensions, consisting in the editing of a document named SIM (Stima di Impatto Multidimensionale – Multidimensional Impact Estimate), which synthesizes the current available evidence about the technology itself. Thus, the report, written by domain experts identified by the NVP-CI, includes the scientific base for the next Appropriateness Judgment provided by the TTRAM.

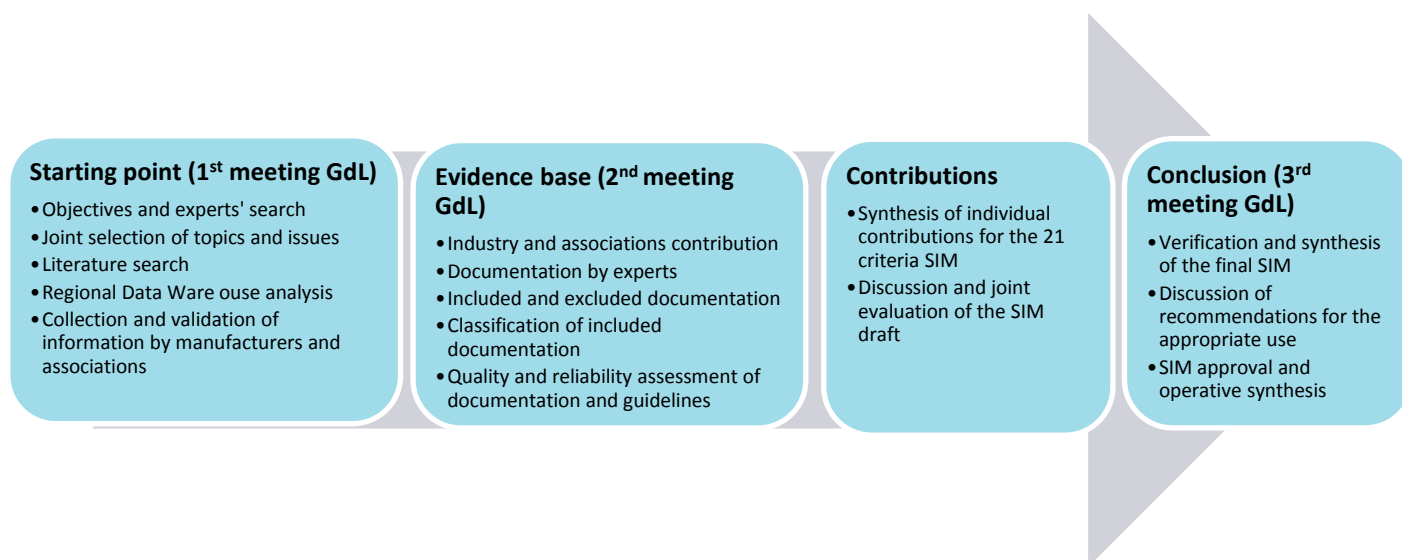


Figure 4.3 - Example of Assessment workflow

In this context, the technical evaluation is structured in a way more complex than the one in the prioritization phase, as here the elements to take into consideration are the combinations of the hierarchy of Dimension, Criterion, Topic and Issue. Not all the elements have the same importance, nor are essential for the production of a complete evaluation. In fact, the nature of the technology, the objectives and the time allotted for the evaluation may require different levels of detail. More specifically, even though all Dimensions and Criteria have always to be documented and taken into account during the decision making process, not all the Topics and Issues can be selected in the SIM. Thus, the choice of which Topics/Issues to document is made by both the panel of experts during the technical evaluation and by manufacturers, who provide their own SIM version, as described later in this paragraph.

The SIM form is composed by three subparts:

- SIM Objectives: providing the general and specific purposes of the evaluation;
- SIM Evidence Base: including the documentation taken into account for the technical evaluation;
- SIM Criteria: collects all the information for each criteria of evaluation.

SIM Objectives

In this first section, objectives defined regard the context and contingencies of the technology itself, clarifying these aspects according to the PICO perspective, namely:

- Patients: referring inclusion and exclusion criteria for the treatment;
- Intervention: regarding which typology if procedure is described;
- Comparisons: describing what is the intervention compared to, such as medical treatment or other surgical procedures;
- Outcomes: differentiated according to their duration and their origins,
 - Short-term effectiveness outcomes
 - Short-term safety outcomes
 - Short-term patient-reported outcomes
 - Short-term technical performance outcomes
 - Long-term effectiveness outcomes

Furthermore, general objectives regard the healthcare area of interest, while specific objectives are related to the expected use of the technology. These information are thus drawn up by the NVP-CI Coordinators in a first draft of the SIM Objectives, which is then validated by the General Healthcare Directorate.

At this point, the NVP-CI Coordinators search for potential domain experts to propose to the General Healthcare Directorate, who will form the experts panel (GdL). The list is filled up with experts in the field of epidemiology, clinic, healthcare economics, and also professionals such as nurses, lab technicians, engineers, administrative officers, etc.; possibly, experts from patients or citizens associations may be involved as well. Suggestions come from healthcare and academic organizations contacted by the General Healthcare Directorate, or by NVP-CI and TTRAM members.

However, it's worth noting that, in this specific context of the Lombardy Region, citizens and patients associations' involvement is low, since members still have to discuss and clarify the level of involvement (advisory or participative during the deliberation phase), the levels of competence and

expertise which enable participants to assume a proactive role, and the in the field training necessary to properly master the process.

Each expert has to provide his/her curriculum vitae, a non disclosure agreement, committing him/herself in not divulging his/her activity and confidential information before the assessment ends, and a conflicts of interest agreement. The latter occur when the individual may personally benefit of public or professional activities' outcomes, thus the professional judgment regarding a primary purpose (for instance, healthcare and clinical benefit maximization and adverse events minimization) is unduly affected by secondary interests (for example, personal or professional interests of individuals or companies, which are strongly different from the primary outcome of the assessment, may be a profit) (Thompson, 1993). Secondary interests of each individual taking part in the different evaluation phases cannot be eliminated, but however can be identified, appraised and taken into account to manage the influence of these points of view on the primary outcome. Once the final list of domain experts is defined by the General Healthcare Directorate, the NVP-CI examines the contact and assigns a risk level to each specialist according to the following encoding:

- Level 1 when the expert doesn't present any conflicts of interest for the technology under evaluation not for possible competitors;
- Level 2 when the expert may present conflicts of interest, both with the company presenting the request and with possible competitors;
- Level 3 when there is documentation which proves the existence of conflicts of interest, and when this conflict may affect the technical contribution itself.

If all the components assign risk level 1, the expert will take part to the assessment, while if all assign risk level 3, the expert will be excluded; in case of in-the-middle situations with level 2 attribution, a further judgment is requested to other NVP-CI components, in order to reach a consensus about lowering the risk to level 1 or increasing it to level 3.

Furthermore, two experts are chosen by the NVP-CI as Coordinators of the panel, approving the SIM Objectives for the next purpose of collecting the elements of the technical evaluation.

SIM Evidence Base

The starting point of the full assessment is the systematic review of scientific evidence. The experts are required to search for high quality contributions in databases of primary studies (e.g. MEDLINE; Embase, Cochrane Controlled Trials Registry, Clinicaltrials.gov) and of secondary studies (e.g. Cochrane Reviews Database, websites of HTA agencies such as CADTH, HAS, NICE), specifying the

research strategy and the criteria for inclusion and exclusion of contributions. A retrospective analysis is then provided from the Regional Data WareHouse (DWH), where all administrative healthcare information, derived by hospitalization or outpatient clinics' archives, are available.

During this phase, an important enabling instrument helps experts in dealing with the amount of documentation to examine: a link to Zotero, an open source and cloud based citation manager, is added to the Assessment pages on the internet portal, in order to directly reach the databases' results, thus reducing the amount of contents on the portal, and to avoid copyright issues, as pdf files are downloadable only under proper licenses purchased by experts for each scientific journal.

The Evidence Base will form a organized, validated and credible collection identified by the literature search, which have to be critically performed in order to remove all commercial or financial interests. Furthermore, a proper definition of ideal and real pathways through patients' treatment is needed: the ideal pathway is referred to facts examined under a controlled context (far from the actual possibilities of practice), while the real pathway is an analysis of what really happens (far from the ideal conditions of research).

In line with this rationale, the resulting publications are registered according to the source (documentation provided by manufacturers or independent documentation) and the typology of study design – randomized controlled trials, observational studies, economic models, Budget Impact Assessment Analyses, systematic reviews, meta-analyses, etc. Clinical guidelines are then added as they provide a systematic collection of rules and regulatory principles: however, guidelines require particular attention when interests of specialists are not declared, are declared in a insufficient way, or are not properly taken into account by regulators, clinics and patients when having to follow them. A pragmatic approach to minimize the risk of low credibility of guidelines, which is already embraced in the Lombardy Region mindset, consists in the following steps (Guyatt, et al., 2010):

1. Associate equal relevance to conflicts of intellectual and financial nature, and arrange explicit criteria for both of them;
2. Ensure that the primary responsibility of editing each chapter of guidelines is in charge of an expert without relevant conflicts;
3. Enable experts with intellectual or financial conflicts to collect and interpret the scientific documentation, but limit the development of recommendations only to those ones who show not having important conflicts.

After a proper classification of the scientific documentation, relevant included contributions are assessed by the panel of experts according to the completeness, consistency, relevance and validity

of evidence using distinct assessment models for epidemiological documentation, clinical outcomes, economic/organizational documentation, budget impact analysis, which distinguish between research background (Trial World Evidence, TWE), such as randomized studies, reviews and meta-analyses of randomized studies, or clinical practice background (Real World Evidence, RWE), such as observational non randomized studies, registries, clinical audits. Thus, each study is graded with a synthesis indicator on a 1-5 scale according to the degree of (i) scientific validity, and (ii) applicability to Lombardy Region of these findings, where 1 stands for the higher level and 5 for the lower level of certainty and robustness degree of recommendations. An example of evaluation tables is provided in Annex E. The quality of guidelines is assessed thanks to the GET5 or the AGREE algorithms, which consist in answering some questions about the level of updating, the credibility, the transparency, and the completeness of the guideline itself.

Finally, each contribution is collected by the General Healthcare Directorate in the SIM Evidence Base, which will be shared among experts for approval.

SIM Criteria

As previously mentioned, all project Coordinators select topics and issues appropriate for the specific assessment and indicate reasons for the exclusion of non relevant ones. The decision will be published with the related documentation at the end of the assessment phase. The scientific Evidence Base is then associated to one or more criteria, which are distributed among the experts: criteria 1 and 2⁸ are in charge of the panel of experts' Coordinators, while the remaining 19 criteria are split between experts by the other NVP-CI and TTRAM Coordinators, so that each specialist evaluates the scientific studies according to his/her view about their relevance for the criterion/criteria assigned. An important tool which is aimed at sharing opinions and question is the forum on the new internet portal: as previously stated, a direct link from each page of the assessment steps connects the task with the confidential online discussion and sharing of information through a proper thread. In this way, members and Coordinators can directly interact among each other and instantly build part of the final report. It's worth noting that this tool has been thought for immediate use of the panel of experts, but other sections are open for NVP-CI and TTRAM members' contributions.

All the answers to included issues are reported in a shared document, the SIM Criteria, which will be later used for the appraisal of the evidence by the TTRAM. In doing so, the VTS-HTA makes a relevant diversion from the EUnetHTA Core Model by incorporating a further level of analysis in-between

⁸ C1: Completeness and consistency of documentation; C2 Relevance and validity of documentation.

dimensions and topics, i.e. criteria, as previously shown in Table 4.2. The integration of EUnetHTA elements and EVIDEM criteria allows translating the outcomes of data collection (i.e. answers to issues) into appraisal (i.e. Multi-Criteria Decision Analysis) in the VTS process. Answers to issues are used to quantify criteria which, in turn, are used for appraisal. Specifically, once the expert provides answers to each issue in a criterion, his/her contribution is sent to one or more assessment Coordinators who (1) verify the clarity of issue assessment, (2) combine experts' contributions into a shared document and (3) present the consolidated SIM to the appraisal committee, the TTRAM, which will shape a final decision on the technology (Radaelli, et al., Working paper).

4.4.3 Appraisal

The last phase of the VTS-HTA process is the determination of the Appropriateness of use Judgment of a specific technology in the SSR context.

Thus, the body entitled of the evaluation of Appropriateness of use is the Regional Technical Roundtable for Medical Appropriateness (Tavolo Tecnico Regionale per l'Appropriatezza in Medicina – TTRAM), which is divided in four equipotent subgroups randomly associated each year to the evaluation for a specific technology: each subgroup is coordinated by a Coordinator, who is chosen among the TTRAM components not belonging to the subgroup and, together with the General Healthcare Directorate, has to coordinate different activities, as depicted in the workflow below.

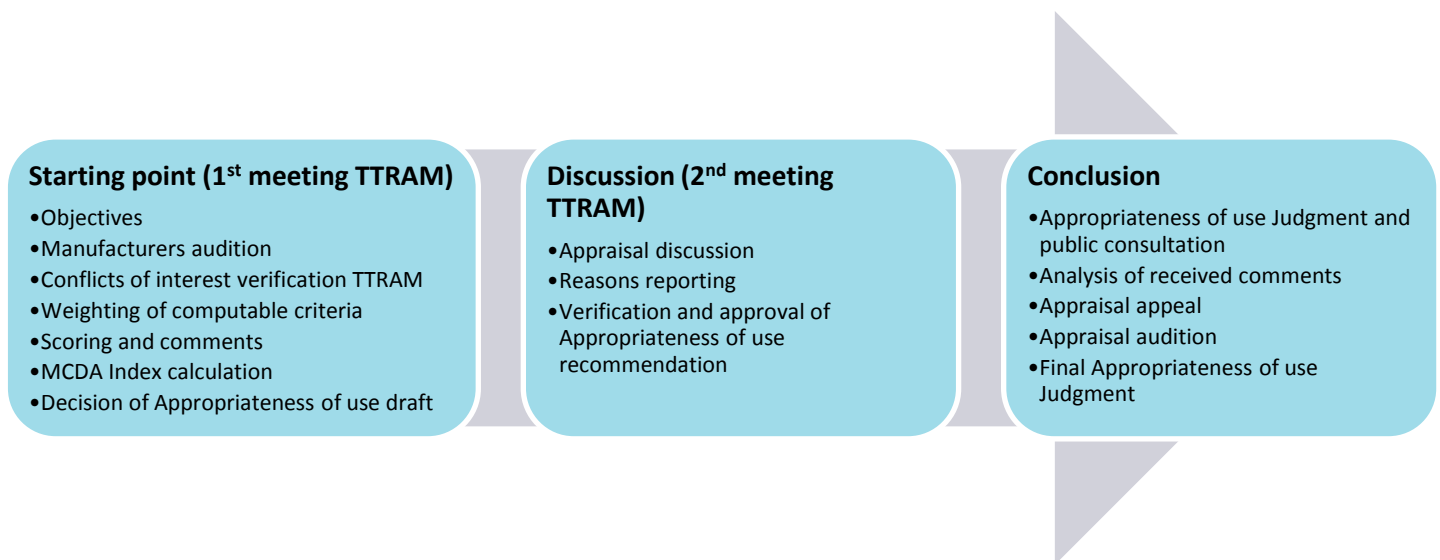


Figure 4.4 - Example of Appraisal workflow

Starting point

During the first meeting of the TTRAM, the SIM Objectives is examined and shared, then the SIM Criteria is assigned by lot to one of the four subgroups. The first task refers to the anticipatory weighting, through the online form on the internet portal, of each one of the 15 computable criteria,

according to a scale that expresses the level of relevance from 1 (higher value) to 15 (lower value), being careful of not assigning the same weight to two different criteria.

Only after this step, the SIM Criteria can be examined by the TTRAM members, then both scores and related comments are attributed to each criteria; scores are defined with a semiquantitative scale, ranging from 0 to 3, where values are explicitly described for each criteria. For instance, in the criterion C1 (Completeness and consistency of documentation) scores mean:

- 0 = the whole documentation is of low quality
- 1 = part of the documentation is of low quality
- 2 = part of the documentation is of moderate quality, the rest is of high quality
- 3 = the whole documentation is of high quality

On the other hand, to the 6 intrinsic criteria are directly associated qualitative judgments, considering three choices: negative impact (if adopted, the technology would be only partially cost-opportune), no significant impact (if adopted, the technology wouldn't cause inefficiencies in the appropriate use of the available budget), or positive impact (if adopted, the technology would improve resource allocation and technical efficiency). Afterwards, the TTRAM Coordinators will analyze consistency of intrinsic criteria and related comments, in order to provide an overall qualitative analysis to the draft of the Appropriateness of use Judgment. As a matter of fact, each intrinsic criterion can add important clues to the overall appraisal, but their inclusion in the linear additive equation would make the MCDA spurious. The appraisal of implicit criteria is, in fact, 'subjective' and contextual while the MCDA manifests 'objective' and evidence-based impacts of the technology.

The 15 explicit criteria can thus be treated in a linear additive equation, in order to calculate the Multi -Criteria Decision Analysis Index as follows:

$$\mathbf{MCDA\ Index\ (technology\ }j) = \sum_{i=1}^{15} [\mathbf{weight}^9(\mathbf{criterion\ }k) \times \mathbf{score\ (criterion\ }k, \mathbf{technology\ }j)]$$

An example of graphic result of the MCDA Index, which is important for the multidimensional impact estimate, is provided in the following figure:

⁹ In the MDCA Index calculation, weights are considered normalized, i.e. their sum must provide result 1.

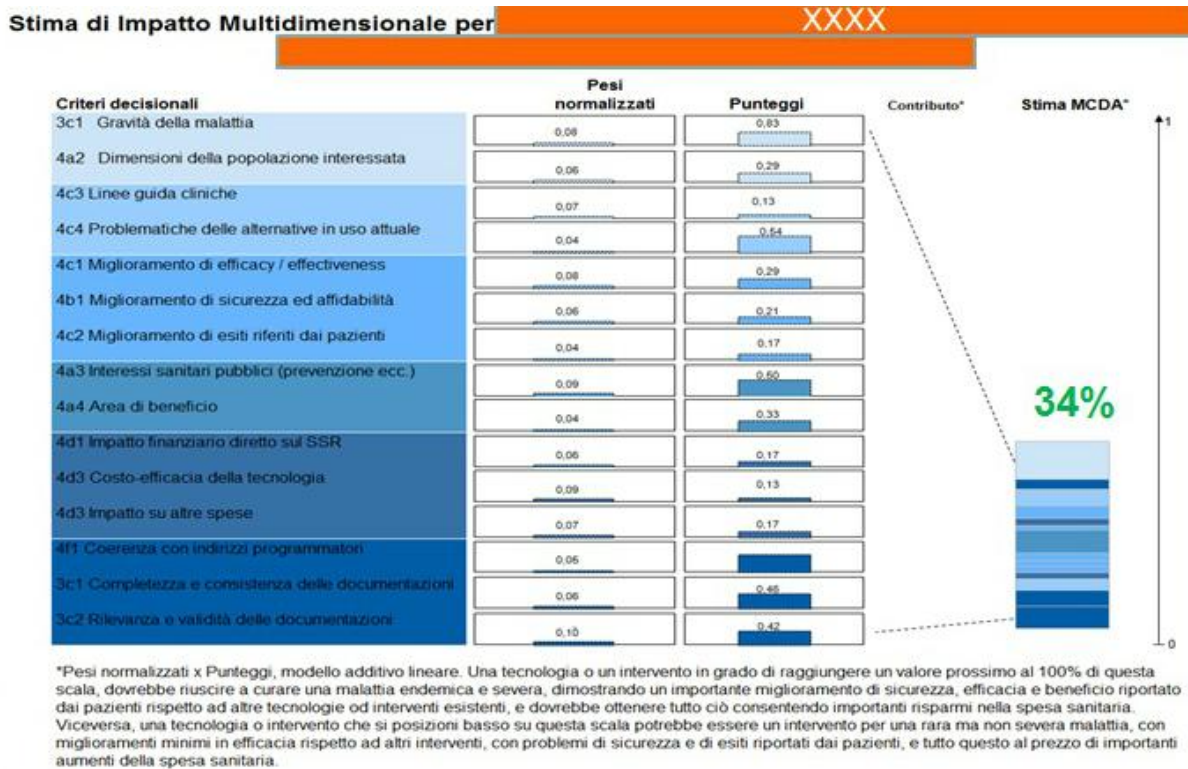


Figure 4.5 - Example of MCDA Index calculation

A high MCDA Index result represents a technology which would treat a serious endemic disease, with remarkable improvements shown in efficacy, safety or patient reported outcomes compared to the limitations of the existing approaches, and resulting in relevant savings for the healthcare system. A low MCDA Index result represents a technology which would be employed with rare diseases or non severe diseases, with limited information showing few improvements in efficacy or higher safety problems compared to current technologies, and resulting in a higher increase of expenditure for the healthcare system. However, the result can be different, according to both the performance of the technology under evaluation for each criterion and its related weight.

Discussion

The final SIM, the results from the MCDA Index calculation and the final decision draft are provided at the second TTRAM convocation. During the meeting, the project Coordinators remind the objectives of the evaluation, to which the activities of discussion, integration and approval of the decision follow, otherwise the decision is postponed for reexamination of the documentation, no longer than two weeks after the second TTRAM meeting.

The minutes of the second meeting is then approved by each TTRAM component, and suggestions for integration are justified and shared with the TTRAM itself for final approval.

Conclusion

The decision about the Appropriateness of use of the technology is made by the TTRAM and approved by the General Healthcare Directorate, which verifies the information about eligibility of the technology for reimbursement, monitoring and controls according to the applicative procedures established by the Lombardy Region.

The outcome of the Appropriateness of use Judgment can be:

1. Appropriate technology, according to conditions and contexts specifically adapted;
2. Potentially appropriate technology, subjected to verification of the additional documentation (for instance, the completion of a clinical study), in charge of the request applicant;
3. Not appropriate technology.

Appropriate and non appropriate technologies are then monitored with specific controls in order to guarantee the respect of adopted decisions.

After the integration of comments and proposal of integration, the final decision about the Appropriateness of use Judgment is released by the General Healthcare Directorate on the Regional website www.sanita.regione.lombardia.it for public consultation, in order to collect remarks or contributions by citizens, professional and organizations which are not directly involved in the technology assessment process. After twenty days, comments are assembled by project Coordinators for possible reconsideration about the Judgment, which has to be provided within the next ten days. The decision is contextually communicated to manufacturers, competitors and to those companies with potential interests, thus, should the Appropriateness of use Judgment have negative result, the procedure of appeal gives the opportunity to producers to further discuss the relevance of its product, thanks to an additional audition and judgment.

Lastly, when both public consultation and possible appraisal appeal are concluded, the final decision on the Appropriateness of use of the assessed technology is adopted with a formal Regional act: Regional Deliberation (Delibera di Giunta Regionale – DGR) and General Healthcare Directorate Decree (Decreto di Direzione Generale – DDG).

5. VTS-HTA Case Study: Patent Foramen Ovale (PFO)

The application of the VTS-HTA framework actually started at the end of 2010, when the Lombardy Region identified some technologies, reported by the RIHTA (Rete Italiana HTA), needing appropriate assessment. From its inception, 29 technologies have been signaled – 12 biomedical devices, 11 drugs, 4 high technologies and 2 food-related products.

So far, six proposals were desk-rejected as they were straightforwardly ineffective, risk-harming or redundant while four proposals are currently awaiting prioritization, as shown in the table below.

1. Desk-rejected technologies		2. Technologies awaiting prioritization
Biomedical devices		Biomedical devices
SMATH for back pain	March 2011	RHEOS for hypertension
Protheses for erectile dysfunction	May 2011	EarlySense – EverOn
Oncotype DX	May 2011	
MAMMAPRINT	September 2011	
Other technologies		Territorial drugs
Nestlé Impact Oral	January 2012	Antidepressants
Special food for Parkinson	May 2012	Inhibitors of proton pump

Table 5.1 - Desk-rejected and awaiting prioritization technologies

The remaining 19 proposals have been admitted to the assessment: 12 proposals are recent and are still at the early stage of experts identification, 2 have passed, instead, to data collection stage, 2 more to the redaction of MIEs and 3 are already in the appraisal stage, awaiting a final decision.

Among those technologies at their final appraisal stage, statins for instance, the phase of weighting criteria has already been concluded in May 2012, while the scoring activity in order to calculate the MCDA Index and the classification of related comments are under completion. Regarding the TAVI procedure, the SIM has been completed in June 2012 and the weighting phase has been started. As previously stated, most of the other evaluations are at their assessment phase, searching and selecting experts, while others are even further, completing the literature search and the Evidence Base.

Among all the technologies under evaluation, the opportunity of investigating the intervention for Patent Foramen Ovale (PFO) closure in adult patients, which is in the middle of completion of the assessment phase, was presented, thus it was interesting to collect all the information available about the pathology and merge the theory of models, explained in the previous chapter, with an applied study, describing both how the process actually works and gradually progresses, and what have been the incoming interactions among actors. When a new framework is under development and all the stakeholders have to be involved at their higher level of engagement, guaranteeing the

conceptual model validity thanks to practice is the first step to show that a transparent and operable instrument is ready to include evidence and assure appropriateness.

5.1 PFO Closure Procedure: Policy Question

The patent foramen ovale (PFO) is a congenital heart anomaly very common among general population. During fetal development, the foramen ovale, formed by a space between the septum secundum and the septum primum, allows blood to pass from the right to the left (from the umbilical vein to the fetal arterial circulation) without passing through the lungs. After birth, increased left-sided pressures in concurrence with decreased right-sided pressure presses the septum primum (from the left) across the septum secundum (arising from the right). In time the two membranes fuse. Failure of the membranes to fuse can occur in about 25% of the population. In this group, the foramen ovale remains patent, thereby allowing communication between the right and left atria, as exemplified in the figure below.

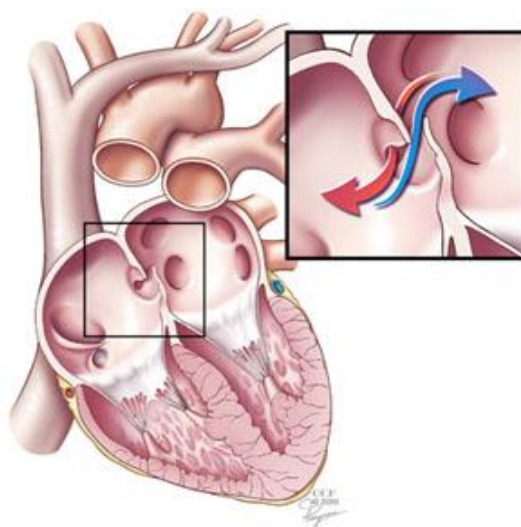


Figure 5.1 - Patent Foramen Ovale illustration

In theory, increased right-sided pressures can result in a right to left shunt, which is a cardiac transit that allows blood to flow from the right heart to the left heart, and subsequent paradoxical emboli, a stroke that occurs due to the unlikely, but possible, migration of a blood clot from a large vein (Deep Venous Thrombosis), into the arteries that bring blood to the brain. The prevalence of PFO appears to decline with age, however, this may be secondary to a greater incidence of mortality among patients with PFO (Bailey, et al., 2004).

Stroke is one of the leading causes of serious mortality and long-term disability, however in approximately 40% of these events occurring to younger adults (meaning aged <55 years) an etiology (i.e. cause) cannot be determined, and these are referred to as cryptogenic strokes. Patent foramen ovale (PFO) has become increasingly implicated as a risk factor for cryptogenic stroke and transient

ischemic attacks (TIAs), however optimal management of these patients remains controversial (Homma, et al., 2002). Patients with PFO may be susceptible to atrial arrhythmias with possible atrial thrombus formation and PFO can serve as a conduit for paradoxical embolisation, as previously mentioned. Other clinical problems, such as migraine headaches, decompression illness in divers, and platypnea orthodeoxia, a rare syndrome consisting of hypoxemia and shortness of breath upon assuming an upright position, have all been associated with PFO, but the exact correlation is poorly defined (Ghosh, et al., 2007). There is still controversy about the presence of a PFO being a cause of stroke in older patients, as usually others can be the reasons for thromboembolic events, such as hypertension or atrial fibrillation.

The most common procedures for detection of a PFO are Transthoracic Ecocardiography (TTE), Transesophageal Ecocardiography (TEE) and Transcranial Doppler (TCD). Computed tomography and magnetic resonance imaging do not currently achieve the sensitivity required for broad clinical use. TTE is performed after peripheral-venous administration of a contrast agent (usually agitated saline solution or gelatin-based plasma expander): the diagnosis of PFO can be made when one or more bubbles appear during the first three cycles after the right-sided opacification in the left atrium or ventricle. The examination should be performed at rest, then with a Valsalva maneuver, which is a procedure that significantly increases the sensitivity by increasing the right-atrial pressure. With TEE, passage of the contrast agent through the PFO channel can be visualized directly and the functional right-to-left shunt evaluated. Patients with cryptogenic stroke show more pronounced contrast agent passage than patients with stroke of other origin. TEE is a semi-invasive method requiring local anesthesia and sedation and thus patient monitoring, however it is associated with a very low complication rate. During Transcranial Doppler Ultrasound (TCD), the number of microembolic signals caused by bubbles in the middle cerebral artery is counted and allows for a qualification of the right-to-left shunt. An alternative method for those not familiar with TCD is the detection of microbubbles in the internal carotid or vertebral arteries. The sensitivity of TCD is comparable with that of TEE, and in individual patients, TCD may even reveal small shunts missed by TEE (Handke, et al., 2009).

Transoesophageal echocardiography is superior to transthoracic echocardiography (TTE) for the detection of potential sources of cardioembolism. TTE identifies sources in about 25% of patients with clinically apparent cardiac disease, but its yield in patients without cardiac signs or symptoms is less than 10%. Transoesophageal echocardiography detects a source of cardioembolism in as many as 57% of patients with unexplained stroke. Transcranial Doppler sonography is an alternative method of detecting a PFO and is considered by some to be superior to the use of two-dimensional

echocardiographic imaging of the atrial septum after intravenous injection of saline contrast medium (Ghosh, et al., 2007).

The management of PFO to date has revolved around three treatment options: medical treatment with anticoagulation or antiplatelet therapy, surgical closure, and percutaneous closure.

- Medical therapy involves anticoagulation or antiplatelet therapy with either warfarin, aspirin, or clopidogrel in combination or alone. In light of major bleeding complications, anticoagulation is a problem when considering the life expectancy of young patients. When comparing drugs used in medical therapy, both observational and randomized data are consistent and suggest that, despite the increased risk of associated hemorrhage, anticoagulants are superior to antiplatelets for secondary prevention of stroke recurrence (IR ratio=0,42; 95% CI, 0,18–0,98), although the strength of evidence would be considered low to moderate by conventional criteria for assessing the overall strength of a body of evidence (Kitsios, et al., 2012) (Orgera, et al., 2001).
- Surgical closure has become rare in recent times with the advent of percutaneous PFO closure methods: this procedure involves sternotomy with direct closure of the PFO under cardiopulmonary bypass, thus is often not a popular option with young patients, furthermore it also carries a measurable risk of open heart surgery (Bailey, et al., 2004).
- Percutaneous closure is implemented by introducing a device via femoral vein through a catheter into the heart and across the patent foramen ovale: the closure device is then inserted through the defect thanks to the delivery sheath and released, thus closing the foramen ovale (NICE, 2005). Since its first introduction in the early 1990s, percutaneous PFO closure has been showed safe and feasible in numerous studies, even in older patients (i.e. with age > 55 years) using a variety of devices. The reported success rates varied between 90 and 100%, with complication rates between 0 and 10%. Complete PFO closure was reported in 51–100% of patients, and yearly recurrence rates of ischaemic strokes and TIAs varied between 0 and 3,4%. However, unlike medical therapy, many complications are related to the transcatheter device closure, which have been reported in numerous observational studies. The major complication rate ranges between 0,2% and 1,5% for procedural-related death, hemorrhage requiring transfusion, cardiac tamponade, need for surgical intervention and fatal pulmonary emboli. Minor complications including bleeding not requiring transfusion, periprocedural atrial arrhythmias, transient atrioventricular node block, device arm fractures, device embolization, thrombosis, arteriovenous fistula formation and femoral hematomas range from 7,9% to 11,5% (Khairy, et al., 2003) (Spies, et al., 2008). Newer

percutaneous devices and smaller catheters have led to a decrease in reported major and minor complications. The incidence of atrial fibrillation after device closure of a PFO is estimated to be 2,5% annually, but this depends on the device used (Tobis, et al., 2012).

Focusing on the latter treatment, the closure device usually consists of two parallel discs of different diameters resembling umbrellas, which are connected by an articulating center post, allowing independent orientation of the left and right atrial umbrella. A fine-wire braided Nitinol mesh, which is contained into the device, is intended to stimulate the body's natural adhesion response for permanent closure of the PFO, and it also provides an immediate barrier to the conduction of emboli before permanent closure (Zimmermann, et al., 2010).

Many devices were developed during last years, as some examples are showed in the figure below:

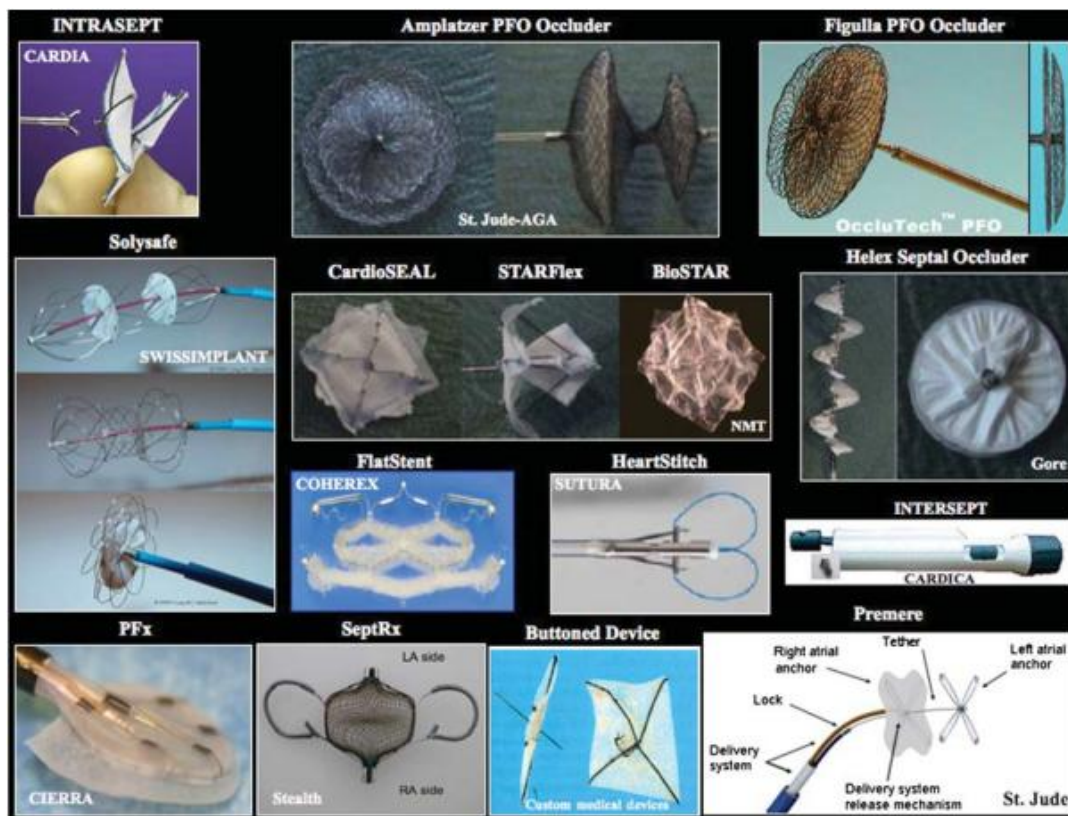


Figure 5.2 - Closure devices and related company names inside pictures

Besides the safety and efficacy of the procedure, the main problem regards its appropriateness of use and the patients who are actually eligible for this treatment, rather than medical therapy, which would be less invasive and less costly.

At the moment, both the only two completed randomized trials, CLOSURE I, investigating cryptogenic stroke with patent foramen ovale, and MIST I, evaluating the effectiveness of PFO closure to resolve refractory migraine headaches, failed to demonstrate the superiority of closure procedure on medical therapy, while highlighting the significant incidence of complications after procedure, such

as an increased rate of atrial fibrillation; however other studies are ongoing, such as the PC-TRIAL, RESPECT and REDUCE stroke trials, and the MIST II, ESCAPE and PREMIUM migraine trials, even though patients enrollment is long and difficult (Dowson, et al., 2008) (Furlan, et al., 2012).

The policy question in Lombardy Region has been presented during a meeting regarding another technology, when some cardiologists reported the issue of PFO closure, as an intervention which caused significant complications in some cases, requiring re-hospitalization expenditures and creating discomforts for patients. Against an arguable effectiveness of the procedure, the General Healthcare Directorate thus decided to deepen this point of question and undertook a rapid literature search on Google Scholar and CADTH (Canadian Agency for Drug and Technologies in Health) HTA reports, which gave the first hints on PFO closure cases.

Furthermore, a consensus document by (Fraser, et al., 2011), published on the European Heart Journal, clarified the ongoing controversies about the effectiveness of the procedure, as some physicians reported that “the therapy is effective despite the lack of appropriate evidence”. In USA, the FDA (Food and Drug Administration), which is the body responsible for evaluation and approval of medical devices, limited the procedure indication to patients with recurrent cryptogenic stroke who had failed conventional drug therapy, however the procedure is currently implemented off-label also in those ones with a first cryptogenic stroke who had not failed medical therapy, and in Europe many devices continue to be implanted.

5.2 Prioritization

After the request on November, 15th 2011, one doctor and the Deputy Director of the HTA Program in the General Healthcare Directorate of Lombardy Region completed an independent Rapid Report (RR) which shed light on the technology under consideration, on comparators and main expected impacts on the system. The information were searched on Pubmed (MEDLINE), Google Scholar and NICE databases, and a first document with the overview about technical and epidemiological relevance, as well as safety and efficacy, was distributed on November, 23rd 2011 to the NVP-CI members, in order to collect personal Priority Judgments. Moreover, two important manufacturers undertook an audition, providing further documentation to the Prioritization Unit.

Anticipatory weighting and then scoring of dimensions, with the addition of comments, were afterwards implemented by the NVP-CI members, in order to perform the Multi-Dimension Decision Analysis and synthesize the Priority Judgment.

Complete evaluations were provided by 9 members, who enabled the General Healthcare Directorate to summarize results and diagrams, as shown in the radar graph below:

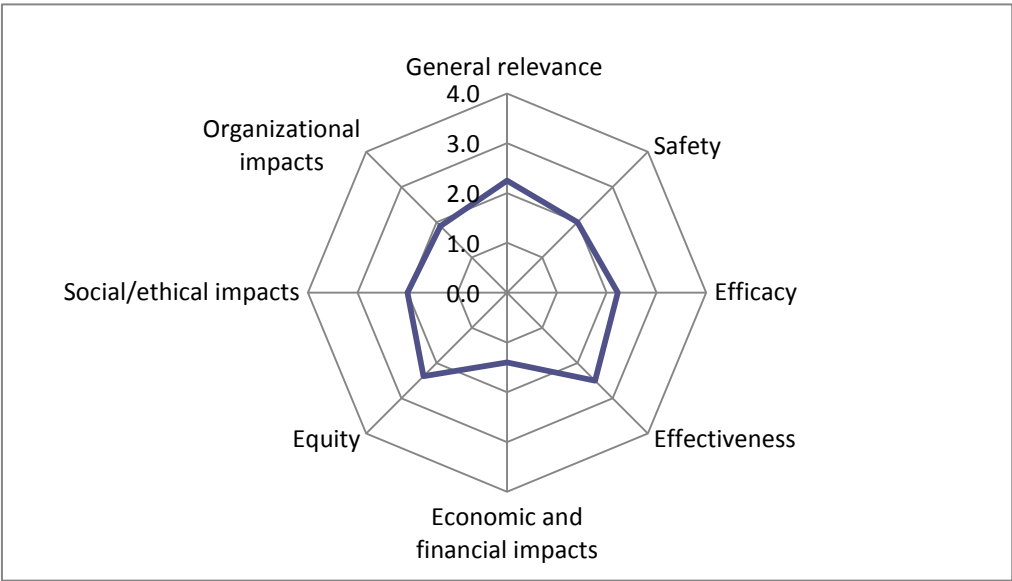


Figure 5.3 - Radar graph of Prioritization Dimensions

A further analysis of means and related standard deviations is depicted in the following figure:

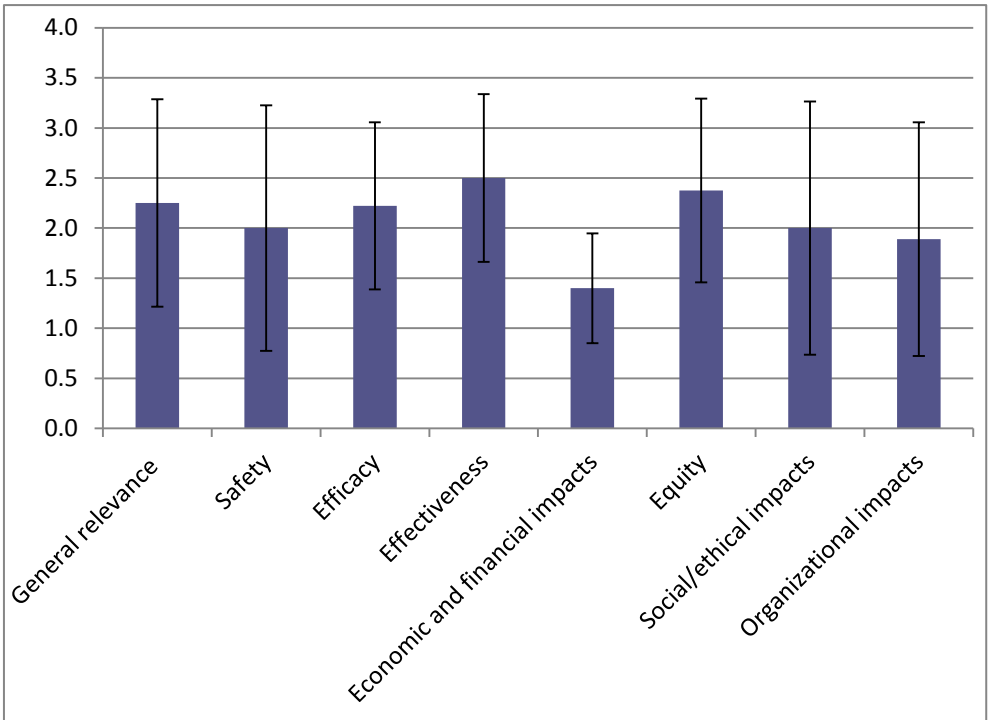


Figure 5.4 - Means and standard deviations of results

The results were considered to be satisfactory in order to proceed to the next phase of the VTS process, moreover the public consultation and the priority appeal were not undertaken.

Finally, during the NVP-CI meeting of March, 15th 2012, two project Coordinators were identified, among members of the group itself, in the quality responsible and risk manager at a hospital of small

dimension, and an epidemiologist at a Local Health Authority; on the other hand, the health director at a cardiology center of middle dimension, and the director of the geriatric cardiovascular department of a middle-dimension institute, were appointed as TTRAM project Coordinators during the meeting of March, 22nd 2012.

The General Healthcare Directorate, supported by the four project Coordinators, identified the typologies of domain experts needed for the following phase, then on May, 11th 2012 it formally requested to the SSR bodies (hospitals, Local Health Authorities, and foundations), to Medicine and Pharmacy university faculties, as well as to NVP-CI and TTRAM members themselves, recommendations for professionals for the Assessment technical evaluation, upon verification of secondary interest by the NVP-CI, as described in the DGR n. 8/7856 attachment.

The final list of proposed experts was defined on August, 3rd 2012, identifying 17 people in the following specialty professions and competences (names cannot be reported due to privacy reasons):

# experts	Competence
3	Haemodynamist cardiologists
2	Heart surgeons
2	Clinical cardiologists, expert in transoesophageal echocardiography
2	Neurologists, expert in cerebrovascular diseases and transcranial Doppler
2	Internists, expert in cerebrovascular diseases
2	Clinical cardiologists
2	Area nurses
1	Neurologist, expert in cerebrovascular diseases
1	Epidemiologist, medical statistician

Table 5.2 - Number of experts and related specialties

5.3 Assessment

During the first meeting of the experts Workgroup (Gruppo di Lavoro – GdL) on September, 17th 2012, the objectives of the evaluation were clarified through the PICO perspective:

- Patients: adults (age > 18 years) with previous cryptogenic stroke (first episode or recurrent), or with migraine;
- Intervention: percutaneous closure of patent foramen ovale through positioning of a permanent implantable endoprosthesis;
- Comparisons: specific medical therapy;

- Outcomes
 - Short-term effectiveness outcomes: stroke/TIA and migraine recurrence;
 - Short-term safety outcomes: bleeding, procedure- or device-related complications;
 - Short-term patient-reported outcomes: health related quality of life (HRQL);
 - Long-term effectiveness outcomes: mortality.

The Assessment objective of writing the SIM, as the technical report to provide the TTRAM with, merges at this point with the Appraisal purpose, which is the verification of the therapeutic properties of the PFO closure intervention according to its actual effectiveness compared to both usual indications and SSR costs; in particular, the main focus of the SIM development is related to:

- Identification of criteria for Appropriateness of use (possible registry of patients' clinical pathway through the treatment of this disease);
- Identification of qualified centers for the implementation of the procedure;
- Revision of the reimbursement tariff.

At this point, the domain experts familiarized with the ontology of the evaluation criteria, which include 64 topics and 139 issues, of which only the appropriate ones have to be selected and included in order to better complete the multidimensional assessment.

Before the determination of a definite literature search strategy, an opportunity was presented to the General Healthcare Directorate by Age.Na.S., the National Agency for Regional Health Services, which proposed a collaboration in order to develop a rapid HTA regarding this Policy question and provided a first Swedish HTA report, edited in 2010, about PFO closure in cryptogenic stroke patients. The collaboration is aimed at undertaking a systematic review and generating a HTA report, which could be mutually useful for the progress of evaluations and strengthen a partnership for future research, by enabling experts of the two organizations to work together.

The rapid HTA Age.Na.S.' framework is different from the VTS dimensions, however there are some common aspects which make comparable the two structures of analysis, as described in the table in the following page:

Rapid HTA Age.Na.S.

1. Technology and current comparators

1.1 Clinical problem

1.2 Epidemiological data

1.3 Treatments and clinical pathways

1.4 Description and regulatory status of the technology

2. Report's objectives: policy and research questions

3. Context overview

3.1 Diffusion of the technology in Italy

3.2 Case study: Lombardy Region

4. Effectiveness and safety

4.1 Methods

4.2 Results of the literature review

4.3 Discussion of results

5. Economic and organizational impact

5.1 Introduction

5.2 Costs linked to misuse of the technology

6. Discussion and conclusion

7. Recommendations

Table 5.3 - Rapid HTA framework, Age.Na.S.

Besides the occasion of accelerating the Assessment phase in Lombardy Region thanks to a more robust documentation and to the support of more focused professionals, the General Healthcare Directorate had already commissioned to one of the Coordinators an exploratory analysis of the Regional Data WareHouse on patients who underwent PFO closure thanks to the “umbrella” prosthesis, in order to corroborate the literature results with contextual information.

Results of this first analysis were provided at the beginning of October 2012, and reported fundamental documentation backing for health programming and for technology assessment itself. Databases used as information basis were the SDO files (Scheda di Dimissione Ospedaliera, i.e. hospital discharge form) from years 2003 to 2011 and the register of assisted patients, thus the main focus of the analysis was to provide descriptive information about the overall extent of the phenomenon in Lombardy Region, the time trend and the territorial distribution. A second objective was the investigation of correlations between previous neurologic conditions and PFO closure procedure, in order to collect data on possible reasons inducing the procedure implementation itself and to provide both effectiveness outcomes and direct economic impact on the SSR information.

A first peculiar issue that emerged was the attribution of different reimbursement tariffs over the years and the use of a different codification for the procedure, which made the investigation more difficult: in fact, until the 31st August 2004, the reimbursement was equal to the 80% (4.778 €) of the total value of the prosthesis (5.972 €), equal to 100% of the total value (5.972 €) from the 1st September 2004 to the 28th February 2007, and from then on the evaluation for reimbursement is

5.873 €. It's important to add that the total cost of the procedure, which depends on the diagnostic instrumentation, amounts around 10.000-15.000 €, including the prosthesis.

The age distribution analysis confirmed that the majority of patients belonged to the 19-60 age range, while only the 15% were aged less than 19 years, as depicted in the figure below:

Frequency Percent Row Pct Col Pct	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total
0	3	3	2	3	4	4	2	2	0	23
	0.04	0.04	0.03	0.04	0.06	0.06	0.03	0.03	0.00	0.34
	13.04	13.04	8.70	13.04	17.39	17.39	8.70	8.70	0.00	
	0.71	0.51	0.29	0.37	0.47	0.44	0.23	0.24	0.00	
1-18	95	116	113	122	119	105	91	118	97	976
	1.42	1.74	1.69	1.83	1.78	1.57	1.36	1.77	1.45	14.63
	9.73	11.89	11.58	12.50	12.19	10.76	9.32	12.09	9.94	
	22.41	19.86	16.21	14.99	13.85	11.44	10.26	14.34	14.59	
19-40	144	168	167	215	233	260	235	169	144	1735
	2.16	2.52	2.50	3.22	3.49	3.90	3.52	2.53	2.16	26.01
	8.30	9.68	9.63	12.39	13.43	14.99	13.54	9.74	8.30	
	33.96	28.77	23.96	26.41	27.12	28.32	26.49	20.53	21.65	
41-60	133	205	270	325	345	403	400	375	304	2760
	1.99	3.07	4.05	4.87	5.17	6.04	6.00	5.62	4.56	41.37
	4.82	7.43	9.78	11.78	12.50	14.60	14.49	13.59	11.01	
	31.37	35.10	38.74	39.93	40.16	43.90	45.10	45.57	45.71	
61-80	48	91	142	146	155	144	157	157	118	1158
	0.72	1.36	2.13	2.19	2.32	2.16	2.35	2.35	1.77	17.36
	4.15	7.86	12.26	12.61	13.39	12.44	13.56	13.56	10.19	
	11.32	15.58	20.37	17.94	18.04	15.69	17.70	19.08	17.74	
81+	1	1	3	3	3	2	2	2	2	19
	0.01	0.01	0.04	0.04	0.04	0.03	0.03	0.03	0.03	0.28
	5.26	5.26	15.79	15.79	15.79	10.53	10.53	10.53	10.53	
	0.24	0.17	0.43	0.37	0.35	0.22	0.23	0.24	0.30	
Total	424	584	697	814	859	918	887	823	665	6671
	6.36	8.75	10.45	12.20	12.88	13.76	13.30	12.34	9.97	100.00

Table 5.4 - Age distribution of patients across years

On the other hand, the residence distribution showed a percentage decrease of patients not coming from the Lombardy Region, who were treated in Lombard hospitals, from 2003 (43%) to 2011 (17%); however about 1/3 of the total patients belonged to the “healthcare mobility” phenomenon. Furthermore, the total number of patients per year has been subjected to fast fluctuations, starting from 424 patients in 2003, reaching a more than doubled peak in 2008 with 918 patients, and finally decreasing to 665 patients in 2011.

Thus, regarding the non Lombard residents composition, the starting point in 2003 was 182, representing almost half of the total hospitalizations, as previously stated, while in 2011 only 111, conferring the highest portion to Lombard patients, who reached 554 hospitalization.

The following table reports in a clear way the yearly trend, according to residence distribution.

Frequency											
Percent											
Row Pct											
Col Pct	2003	2004	2005	2006	2007	2008	2009	2010	2011	Total	
NL	182	227	232	264	273	297	239	246	111	2071	
	2.73	3.40	3.48	3.96	4.09	4.45	3.58	3.69	1.66	31.04	
	8.79	10.96	11.20	12.75	13.18	14.34	11.54	11.88	5.36		
L	42.92	38.87	33.29	32.43	31.78	32.35	26.94	29.89	16.69		
	242	357	465	550	586	621	648	577	554	4600	
	3.63	5.35	6.97	8.24	8.78	9.31	9.71	8.65	8.30	68.96	
Total	5.26	7.76	10.11	11.96	12.74	13.50	14.09	12.54	12.04		
	57.08	61.13	66.71	67.57	68.22	67.65	73.06	70.11	83.31		
	424	584	697	814	859	918	887	823	665	6671	
	6.36	8.75	10.45	12.20	12.88	13.76	13.30	12.34	9.97	100.00	

Table 5.5 - Residence distribution across years (NL - Not Lombard patients; L - Lombard patients)

The distribution of procedures volumes underlines that 7 Lombard high-volume facilities treated the 73% of total cases (range of 293-2209 cases from 2003 to 2011), while the 7 low-volume facilities treated the 0,3% of cases (range 1-5); furthermore, only one hospital treats the 33% of cases, while many facilities implemented the procedure occasionally.

The follow-up reconstruction was possible only for resident patients, specifically 4562 out of 4600, thanks to individual code linking, however data entry errors caused some missing information.

A first evaluation could be undertaken on subgroups of patients aged > 18 years, where different disease conditions were separated, in order to better isolate cryptogenic stroke cases, as shown in the table below:

pfo	ictustia	fa	emo	occlu433	occlu434	caro	Frequency	Percent	Frequency	Percent
0	1	0	0	0	0	0	49340	25.79	49340	25.79
0	1	0	0	0	0	1	21598	11.28	70930	37.07
0	1	0	0	0	1	0	60741	31.75	131673	68.82
0	1	0	0	0	1	1	1506	0.79	133179	69.61
0	1	0	0	1	0	0	4461	2.33	137640	71.94
0	1	0	0	1	0	1	2705	1.41	140345	73.35
0	1	0	0	1	1	0	3489	1.82	143834	75.18
0	1	0	0	1	1	1	1065	0.56	144899	75.73
0	1	0	1	0	0	0	1157	0.60	146056	76.34
0	1	0	1	0	0	1	265	0.14	146321	76.48
0	1	0	1	0	1	0	1777	0.93	148098	77.41
0	1	0	1	0	1	1	66	0.03	148164	77.44
0	1	0	1	1	0	0	134	0.07	148298	77.51
0	1	0	1	1	0	1	65	0.03	148363	77.54
0	1	0	1	1	1	0	121	0.06	148484	77.61
0	1	0	1	1	1	1	36	0.02	148520	77.63
0	1	1	0	0	0	0	10576	5.53	159096	83.15
0	1	1	0	0	1	1	2321	1.21	161417	84.37
0	1	1	0	0	1	0	21796	11.39	183213	95.76
0	1	1	0	0	1	1	275	0.14	183488	95.90
0	1	1	0	1	0	0	903	0.47	184391	96.38
0	1	1	0	1	0	1	348	0.18	184739	96.56
0	1	1	0	1	1	0	941	0.49	185680	97.05
0	1	1	0	1	1	1	155	0.08	185835	97.13
0	1	1	1	0	0	0	372	0.19	186207	97.32
0	1	1	1	0	0	1	47	0.02	186254	97.35
0	1	1	1	0	1	0	951	0.50	187205	97.85
0	1	1	1	0	1	1	25	0.01	187230	97.86
0	1	1	1	1	0	0	29	0.02	187259	97.87
0	1	1	1	1	0	1	7	0.00	187266	97.88
0	1	1	1	1	1	0	46	0.02	187312	97.90
0	1	1	1	1	1	1	18	0.01	187322	97.91
1	0	0	0	0	0	0	2487	1.30	189809	99.21
1	1	0	0	0	0	0	365	0.19	190174	99.40
1	1	0	0	0	0	1	4	0.00	190178	99.40
1	1	0	0	0	0	1	1052	0.55	191230	99.95
1	1	0	0	0	0	1	6	0.00	191236	99.95
1	1	0	0	1	0	0	19	0.01	191255	99.96
1	1	0	0	1	1	0	14	0.01	191269	99.97
1	1	0	0	1	1	1	1	0.00	191270	99.97
1	1	0	1	0	0	0	2	0.00	191272	99.97
1	1	0	1	0	1	0	6	0.00	191278	99.97
1	1	0	1	0	1	1	1	0.00	191279	99.98
1	1	1	0	0	0	0	12	0.01	191291	99.98
1	1	1	0	0	1	0	32	0.02	191323	100.00

Table 5.6 - Patients subgroups and related frequencies

In the first column, the absence (0) or presence (1) of single criteria are reported: PFO closure procedure (PFO), stroke/TIA event (ictustia), atrial fibrillation (FA), cerebral bleeding (emo), pre-cerebral arteries occlusion (occlu433), cerebral arteries occlusion (occlu434), and carotid unblocking (caro). From the results, patients who underwent closure procedure, independently from the stroke/TIA event, were 4001, of which 2487 didn't have any other disease: it's thus evident a problem of procedure appropriateness for this about 50% of patients. According to the analyst's opinion, these cases might be ascribed to possible conditions of migraine or professional divers, who wanted to prevent any cerebrovascular event, even earlier than its first episode.

Cases presenting stroke/TIA without other conditions were 365, indicating a possible cryptogenic stroke; anyway, with a more extensive criterion, other 1052 further cases could be potentially characterized as cryptogenic, when considering that the cerebral occlusion codification didn't exclude the diagnosis of a cryptogenic stroke.

Even though this first analysis represents a strong warning for appropriateness and necessity of disinvestment of those centers which implement the procedure occasionally, further in-depth examinations are needed about patients follow-ups.

Finally, the current guidelines for Italy were added, as clarified by SPREAD (Stroke Prevention and Educational Awareness Diffusion):

- For patients with an ischemic cryptogenetic stroke or TIA and a PFO without deep vein thrombosis or thrombophilic disorders Aspirin 325 mg once daily is indicated.
- For patients with an ischemic cryptogenetic stroke or TIA and a PFO with other indications for oral anticoagulant therapy such as deep vein thrombosis or thrombophilic disorders Warfarin is indicated.
- For patients with an ischemic cryptogenetic stroke or TIA and a PFO with deep vein thrombosis or thrombophilic disorders and contraindications for oral anticoagulant therapy PFO closure is indicated.
- For patients with cryptogenetic stroke recurrence in the presence of therapy with Aspirin or Warfarin, PFO closure is indicated after a multidisciplinary case examination and patient agreement (*Good practice point*).

The management of patients with cryptogenic stroke and PFO is controversial. In some communities, interventional procedures are sharply increasing while in others these are being banned, giving rise to confusing behaviors in patients as well as in the medical community. However, while waiting for

proper scientific documentation, the reimbursement tariff doesn't have to compensate, over a reasonable level, ignorance and missing research.

The Assessment phase is currently at this stage of information collection, while the anticipatory weighting of criteria of the Appraisal phase is being arranged, in order to reach the final Appropriateness Judgment in the end of January 2013.

5.4 Methodology and SIM Reproduction

In order to better understand how the process in Lombardy Region actually works, and to focus on its inefficiencies and issues, the present work shows a simulation of the SIM implementation, which starts from the collection of documentation through the literature search, to the appropriate completion of selected issues, as will be described in depth throughout the next paragraphs.

5.4.1 Literature Search

Thanks to the supervision and suggestions of one of the Coordinators, the literature search was performed on Pubmed (MEDLINE) database, collecting information from both stroke and migraine streams, according to specific inclusion criteria, as follows:

- Language: English, Italian
- Species: humans
- Ages: all adult 19+ years
- Type of article: clinical trial, meta-analysis, practice guideline, randomized controlled trial, review

The first search with the specific direct keywords “patent foramen ovale closure OR pfo closure AND stroke” provided 54 citations, while the second search with “patent foramen ovale closure OR pfo closure AND migraine” provided 22 citations. Abstracts were screened and a further inclusion criterion for articles to be taken into account was the presence of a number of patients > 200, in order to confer more reliability to the study, then other additional documents were provided by references search, according to the Coordinator's indications, resulting in the following process:

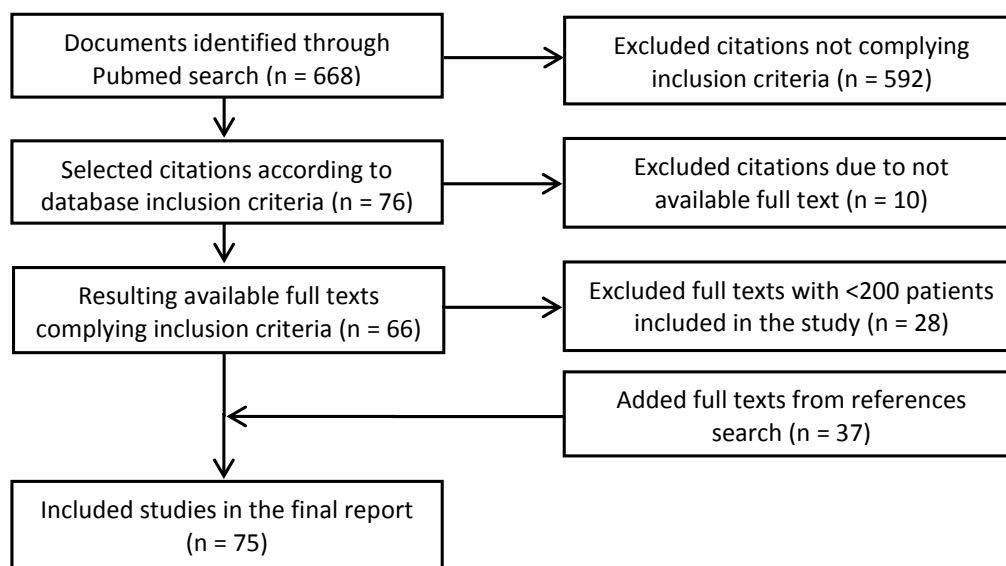


Figure 5.5 - Literature search flowchart

The second phase consisted in clustering the selected articles according to the disease (stroke or migraine) and the typology of studies, namely randomized controlled trials, clinical trials, meta-analyses, practice guidelines, registries (collections of data on devices or drugs usually undertaken by producers themselves) and reviews: results are reported in the following table.

Clusters	# Stroke articles	# Migraine articles
Randomized controlled trial	2	1
Clinical trial	27	5
Meta-analysis	4	1
Practice guideline	1	0
Registry	5	1
Review	24	1
Total articles	63	9

Table 5.7- Clusterization of included studies

Finally, all articles were analyzed and useful information were categorized in tables in order to better cover VTS dimensions and their related issues, focusing on a comparison between the large amount of different data available.

The SIM is provided in the next paragraph: it's important to note that, as common in the actual world of the evaluations, not all issues can be completed only with the documentation available in literature, thus representing a gap which has to be overcome thanks to experts' knowledge and know-how, or through further analyses that the evaluation has to recommend.

5.4.2 SIM (Stima di Impatto Multidimensionale – Multidimensional Impact Estimate)

Codice SVTS/2012/... Data: Data validità: ... Tecnologia Intervention for percutaneous closure of patent foramen ovale (PFO) Nome commerciale: Amplatzer; CardioSEAL; Starflex; PFO-Star; Helex; Angel Wings; Premere Nome produttore: Many
Tipo di tecnologia: Transcatheter seal for PFO tunnel occlusion Patologia ed indicazione: Secondary prevention of recurrent cryptogenic stroke or TIA Primary prevention of recurrent cryptogenic stroke or TIA Exclusion with congenital heart disease clinically evident Ambito di utilizzo: Hemodynamics/heart surgery/interventional cardiology Somministrazione/impianto/modo di utilizzo: transcatheter implantation via trans-femoral vein Durata del trattamento: Lifelong Comparatore(i): Medical therapy, Surgical closure Onere economico della malattia: ...

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D8 – Organizational Impact

- C21 – System capacity, appropriate technology use

Legend:

- RCT – Randomized controlled trial
- SC – Single arm closure study
- SM – Single arm medical study
- C – Comparative study
- M – Meta-analysis
- E – Epidemiological clinical study
- G – Guideline

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Dimension D1: General Relevance

Criterion C1 – Quality of the documentation:

Completeness and consistency of documentation¹⁰

Misura in cui le documentazioni della tecnologia proposta sono complete (ad es. rispettano gli standard scientifici) e consistenti tra le diverse fonti citate.

SOTTOCRITERI e QUESITI: non disponibili.

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Criterion C2 – Quality of the documentation:

Relevance and validity of documentation¹¹

Misura in cui l'evidenza della tecnologia proposta è rilevante per il SSR (in termini di popolazione, stadio della malattia, tecnologie comparatrici, *outcome*, etc.) e valida rispetto agli standard scientifici (ad es. disegno dello studio, etc) e alle conclusioni (accordo dei risultati tra differenti studi). Tutto questo include considerazioni di incertezza (ad es. risultati conflittuali tra diversi studi, limitato numero di studi e pazienti).

SOTTOCRITERI e QUESITI: non disponibili.

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Criterion C3 – Description and severity of illness

Fonti: Revisione della letteratura raccolta con la ricerca bibliografica, recenti revisioni in riviste importanti, libri di testo, ecc.

Da fare:

- Descrivere la malattia (definizione della malattia, dei sintomi, della eziologia, delle co-morbidità e dei rischi associati) e la sua progressione
- Riportare l'impatto della malattia su mortalità, morbidità, qualità di vita
- Dove possibile descrivere gli stadi o i sottotipi di malattia che differenziano i destinatari e/o gli interventi

Da non fare:

- Non includere informazioni epidemiologiche (-> criterio 4a.2 Dimensioni della popolazione)
- Non includere descrizione delle tecnologie o dei trattamenti attualmente utilizzati (-> criterio 4d.2 -> Problematiche delle alternative tecnologie di uso attuale)

SOTTOCRITERIO: Target Condition

A0001 QUESITO: Which disease/health problem/potential health problem will the technology be used for?¹²

Stroke is the third leading cause of mortality and the most important cause of serious, long-term disability C (Wahl, et al., 2012). The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification subdivides the cause of stroke into five subtypes, on the basis of clinical features and the results of diagnostic tests: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other known cause, and stroke of

¹⁰ **Completezza e coerenza della documentazione. Razionale:** una tecnologia per la quale le documentazioni scientifiche riportate sono complete e coerenti dovrebbe avere un punteggio più alto di una tecnologia con documentazioni incomplete e/o con aree di incoerenza. La qualità delle analisi contribuisce al valore della tecnologia così come un'analisi povera limiterà la comprensione dei dati, e quindi farà scendere il valore della tecnologia. Poiché la qualità dell'analisi potrebbe essere alta ma la validità e la rilevanza basse, queste ultime vengono considerate separatamente nella prossima scheda. Inoltre, la generazione dei punteggi di qualità per completezza / coerenza e per validità / rilevanza delle documentazioni richiede tipi di analisi sostanzialmente differenti: per l'analisi della qualità dei dati riportati occorre una analisi critica verso riferimenti stabiliti da vari standard internazionali, mentre per l'analisi di validità e rilevanza delle documentazioni occorre un'analisi critica nel contesto (sociale, regolatorio, clinico, economico) locale cioè italiano e regionale.

¹¹ **Rilevanza e validità della documentazione. Razionale:** Un intervento per il quale la documentazione è rilevante per la decisione da prendere e valida rispetto agli standard internazionali dovrebbe avere un valore più alto di una tecnologia per la quale la documentazione ha bassa rilevanza e validità. Rilevanza e validità della documentazione contribuiscono al punteggio di un tecnologia così come una limitata validità e rilevanza riduce la confidenza nella capacità della tecnologia di migliorare la salute in un dato contesto.

¹² **DESCRIZIONE:** Definition (naming) of the condition, health problem, disease for which the technology is intended. **FONTE INFORMATIVA:** Medical literature, at the best systematic reviews on mechanism of disease, risk factors, course and prognosis. Developers/ manufacturers view on the potential targets and what they expect/claim from the technology.

unknown cause. Strokes which remain of indefinite cause after an extensive diagnostic workup are classified as cryptogenic, which account for about 30-40% of all strokes **C** (Paciaroni, et al., 2011) .

During the last decade there has been an increasing emphasis on the role of interatrial septal abnormalities including patent foramen ovale (PFO) and interatrial septal aneurysm (ASA) as potential risks factors, since some cryptogenic strokes or transient ischemic attacks (TIAs) may be the result of an embolus from the venous system traversing from the right to the left atrium and into the systemic circulation through the PFO itself, which is a phenomenon known as paradoxical embolism **SM** (Bogousslavsky, et al., 1996). Paradoxical embolism through a PFO was first described in 1877 by Julius Conheim during an autopsy of a young woman with a fatal occlusion of a cerebral artery. He observed that the patient had a significant lower extremity thrombus and a large PFO, which he hypothesized served as a conduit for an arterial embolism that paradoxically started in the venous circulation. The advent of echocardiography improved the understanding of PFO anatomy and detection **R** (Tobis, et al., 2012).

In the phase of fetal development, the foramen ovale, formed by a space between the septum secundum and the septum primum, allows blood to pass from the right to the left (from the umbilical vein to the fetal arterial circulation) without passing through the lungs. After birth, increased left-sided pressures in concurrence with decreased right sided pressure passes the septum primum (from the left) across the septum secundum (arising from the right). In time the two membranes fuse, but their failure to fuse can occur in about one fourth of the population. In this group, the foramen ovale remains patent, thereby allowing communication between the right and left atria. In theory, increased right-sided pressures can result in a right to left shunt (RLS) and subsequent paradoxical emboli. The prevalence of PFO appears to decline with age, while its dimension increases with ageing, however this may be secondary to a greater incidence of mortality among patients with PFO. Furthermore, an atrial septal aneurysm (ASA), a redundant tissue of the atrial septum that protrudes into the left or right atrium with an excursion of ≥ 10 mm and a diameter of the base of the aneurysm of at least 15 mm, as previously stated, has been implicated as an increased risk factor for recurrent stroke; although the overall prevalence of ASA as an isolated abnormality is low, it is common in association with PFO.

Other clinical problems, such as **migraine headaches, decompression illness in divers**, and platypnea orthodeoxia, a rare syndrome consisting of hypoxemia and shortness of breath upon assuming an upright position, have been associated with PFO, but the exact correlation is poorly defined **R** (Bailey, et al., 2004).

Migraine

Previous theories with regard to the etiology of migraines hypothesized that cerebral vasospasm led to brain ischemia and directly produced migraine auras. In addition, stroke associated with migraine was believed to be secondary to such intense arterial constriction that a cerebral infarction ensued directly from the vasospasm. Magnetic resonance imaging and positron emission tomography have subsequently demonstrated that cerebral vasodilatation occurs first, followed by vasoconstriction that is associated with cortical neuronal depression. This inhibition of neurons spreads as a wave from the optical cortex to the motor and sensory cortices, leading to transient neurological deficits that are identified as migraine auras. Approximately 30% percent of migraineurs have headaches preceded by 1 or more focal neurologic symptoms collectively known as aura. Aura symptoms, predominantly localized to the cerebral cortex, can include transient visual disturbances, marching unilateral paresthesias and numbness or weakness in an extremity or the face, language disturbances, and vertigo. The aura will often last for <1 hour **R** (Carroll, et al., 2009).

Given this current concept of migraine physiology, it is hypothesized that a PFO serves as a conduit for the passage of chemical triggers that interact with neuronal receptors in susceptible people. These triggers induce cortical depolarization and concomitant transient neurological deficits, leading to the clinical phenotype of auras and migraine headache. The PFO permits the chemical triggers to reach the brain without entering the pulmonary circulation where degradation of these products would normally occur **R** (Tobis, et al., 2012).

Decompression sickness in divers and PFO

Decompression sickness (DCS I—musculoskeletal; DCI II—neurologic) arises from nitrogen and oxygen gas formation in various body tissues at increased ambient pressure. Gas passage from the systemic venous to arterial circulation can occur due to either pulmonary barotrauma or intravascular shunting.

Several studies have suggested increased incidence of PFO in divers with DCS. From initial recognition of association of PFO with DCS in 1986, to current reports of PFO closure for divers affected by DCS, differences in outcomes of case series highlight the differences in techniques used to: (1) select and enrol studied patients and controls; (2) clinically diagnose DCS; (3) diagnose PFO; and (4) image “neurologic events”. In light of these limitations, general reviews suggests that: (1) regardless of presence of PFO, increasing numbers of dives may

be associated with increasing incidence of DCS or asymptomatic neurologic events (ANEs); (2) occurrence of ANEs is likely to be common (25–50% of screened patients) in high volume divers; (3) multiple recurrences of DCS II, ANEs, and migraine headaches with aura may cluster in persons with “large shunt volume” PFO (atrial septal aneurysm or spontaneous shunting) **R** (Landzberg, et al., 2004).

A0002 QUESITO: What, if any, is the precise definition/ characterization of the target disease? Which diagnosis is given to the condition and according to which classification system (e.g. ICD-10)?¹³

A cerebral infarct has to be demonstrated by radiological evidence with computed tomography or magnetic resonance imaging. A diagnosis of cryptogenic stroke is accepted by exclusion if further investigation failed to demonstrate another source of embolus **SC** (Bissessor, et al., 2011).

The most common procedures for detection of a PFO are transthoracic ecocardiography (TTE), transesophageal ecocardiography (TEE) and transcranial Doppler (TCD), as further explained below **R** (Handke, et al., 2009).

Transthoracic Ecocardiography (TTE)

For PFO detection, TTE is performed after peripheral-venous administration of a contrast agent (usually agitated saline solution or gelatin-based plasma expander). The diagnosis of PFO can be made when one or more bubbles appear during the first three cycles after the right-sided opacification in the left atrium or ventricle. The examination should be performed at rest, then with a Valsalva maneuver, because this significantly enhances the sensitivity by increasing the right-atrial pressure. Proper performance of the maneuver is essential to avoid false-negative results. Early studies reported sensitivities of TTE compared with TEE of only 30% to 50%, but more recent studies using improved imaging showed a significantly higher sensitivity of ~90% for TTE.

Transesophageal Ecocardiography (TEE)

TEE is the current method of reference for the detection of PFO and ASA. The PFO diameter can be determined by two-dimensional-B-Mode echocardiography or by color Doppler. A larger diameter of the PFO channel is associated with an elevated risk of stroke. Passage of the contrast agent through the PFO channel can be visualized directly and the functional right-to-left shunt evaluated. Patients with cryptogenic stroke show more pronounced contrast agent passage than patients with stroke of other origin. Comparison with autopsy results show a high sensitivity of contrast-enhanced TEE of ~90%, which could be further increased using color Doppler. In some patients, the contrast agent does not reach the area of the PFO after administration via a cubital vein because it is washed out by the inflow of the inferior vena cava. Transfemoral administration of the contrast agent increases the sensitivity in these patients.

TEE is a semi-invasive method requiring local anesthesia and sedation and thus patient monitoring, however it is associated with a very low complication rate.

Transcranial Doppler Ultrasound (TCD)

During TCD, the number of microembolic signals caused by bubbles in the middle cerebral artery is counted and allows for a qualification of the right-to-left shunt. An alternative method for those not familiar with TCD is the detection of microbubbles in the internal carotid or vertebral arteries. The sensitivity of TCD is comparable with that of TEE, and in individual patients, TCD may even reveal small shunts missed by TEE. This can be explained by the better feasibility of the Valsalva maneuver during TCD because sedation is not required. Using TCD, however, the precise location of the right-to-left shunt cannot be determined, furthermore it doesn't provide any information about the anatomy of the atrial septum and associated structures.

Furthermore, there are several methods to quantify the **size of a shunt**. The shunt is quantified by the number of bubbles passing the septum after the injection: grade 0: none, minimal: 1–5 bubbles, moderate: 6–20 bubbles, severe: > 20 bubbles **SC** (Fischer, et al., 2008). The number of microbubbles can be counted with TTE. The Doppler signal across the mitral valve can also be quantified. Similarly, the number of microbubbles can be counted with TE studies. With TCD, high-intensity transient signals also can be quantified. However, any of these methods will be variable because of differences in the amount of bubbles injected, speed with which they are injected, and variations in blood flow pattern in cardiac chambers. Alternatively, anatomic size of a PFO can be measured by TEE. Measurement from a vertical plane view in TE studies correlates well with that by

¹³ DESCRIZIONE: Characteristics of the condition which allow a precise diagnostic and differentiation of the indication for the use of the technology. FONTI INFORMATIVE: Medical literature, at the best systematic reviews on mechanism of disease, risk factors, course and prognosis.

the invasive balloon method, which in general relates to the amount of shunt. However, a PFO is inherently a 3D structure with dynamic opening and closing, as well as a channel-like structure in some patients that makes it difficult to describe the size in 1 dimension **R** (Homma, et al., 2005).

Migraine

Diagnosis of migraine follows criteria of the classification of the International Headache Society (HIS): there are 6 major categories of migraine, which include migraine without aura, migraine with aura and probable migraine (when there is lacking diagnostic information). The importance of a proper diagnosis of migraine determines a significant variation of more than 70% in the estimation of the prevalence of this pathology **R** (Balbi, et al., 2010).

Furthermore, the diagnosis of migraine is purely clinical, and its physiopathology is complex and not fully understood, with both genetic and environmental factors appearing to play an important role. However, in patients with symptomatic PFO, such as paradoxical embolism or decompression illness, a higher prevalence of migraine has been reported **SC** (Wahl, et al., 2010).

Decompression sickness in divers

Standardisation of diagnosis and outcome remains a major obstacle for assessment of treatment for DCS prevention. Typically, more than 50% of high volume divers with ANEs remain asymptomatic, and there are no recognised risks predictive of future symptomatic events. In this context, nonetheless, previously symptomatic or high volume divers with ANEs or with “high risk” anatomic PFO features, who wish to continue diving may warrant closure in centres maintaining closure registries or participation in trials. Intervention for low volume sports divers with PFO without ANEs or symptoms of DCS, regardless of anatomic concerns, remains unfounded at the present **R** (Landzberg, et al., 2004).

A0003 QUESITO: Which are the known risk factors for acquiring the condition?¹⁴

Risk factors related to stroke and PFO belong, on the one hand, to morphological characteristics which increase the chance of developing paradoxical embolism, while on the other hand to predictors more connected to the lifestyle of people.

Besides a large PFO, a spontaneous right-to-left shunt, and the presence of ASA, which is 10 times less common than a PFO, less explored morphological factors are redundant Eustachian valve or Chiari's network **R** (Ballerini, et al., 2007).

The anatomic size of the PFO is a potential risk stratification variable, since larger PFO may be associated with greater volumes of paradoxical blood flow and allow passage into the arterial circulation of larger clots more likely to cause symptomatic stroke. Several case-control studies have found that larger PFO size is associated with both cryptogenic stroke, but others have failed to confirm this finding. Similarly, other studies have found that stroke patients with PFO have a greater frequency of right-to-left shunting at rest compared with controls **R** (Anamnat, et al., 2011).

ASA has been associated with cerebral ischaemic events in numerous case-control studies. The combination of PFO and ASA must account for this and constitutes a particularly high-risk situation with a relative risk of 16 (95% CI 3–86) comparing ischaemic stroke with non-stroke control subjects, and a relative risk of 17 (95% CI 2–134) comparing cryptogenic stroke with known stroke cause control subjects (age >55 years) **M** (Overell, et al., 2000). Thus, as already mentioned, ASA may facilitate paradoxical embolism by leading to a more frequent and wider opening of the PFO channel or by promoting a right-to-left shunt by redirecting flow from the inferior vena cava towards the PFO **R** (Meier, et al., 2012).

Other stroke risk factors belonging to the second category are arterial hypertension (blood pressure of > 140/90 mm Hg at least twice before stroke or already when under treatment with antihypertensive drugs), diabetes mellitus, current cigarette smoking, current use of oral contraceptives or estrogen replacement therapy, hypercholesterolemia, alcohol use, mitral valve prolapse and a history of migraine **C** (Paciaroni, et al., 2011).

A0004 QUESITO: What is the natural course of the condition?¹⁵

¹⁴ DESCRIZIONE: Self-explaining. The prevalence of different risk factors might be different in different geographic areas. FONTI INFORMATIVE: Medical literature, at the best systematic reviews on mechanism of disease, risk factors, course and prognosis.

¹⁵ DESCRIZIONE: For example stages of the disease which can be object of different interventions. FONTI INFORMATIVE: Medical literature, at the best systematic reviews on mechanism of disease, risk factors, course and prognosis.

Percutaneous PFO closure eliminates the potential pathway of paradoxical embolism, thus avoiding both recurrent cerebrovascular and thromboembolic events **R** (Meier, et al., 2012).

Furthermore, some findings suggest that PFO might be related to migraine, at least in a sizeable proportion of migraineurs. This led several experts to postulate that, in some migraineurs, headache attacks may be triggered by a certain amount of a yet-unidentified substance (vasoactive chemicals or microemboli) bypassing the lung filter through a shunt, mostly a PFO **SC** (Wahl, et al., 2010).

A0005 QUESITO: What are the symptoms of the disease?¹⁶

The diagnosis of ischemic stroke is defined as a sudden new focal neurological deficit lasting > 24 hours with evidence of brain damage on computer tomography or magnetic resonance. A TIA is classified as a transient episode of neurological dysfunction lasting < 24 hours with or without evidence of brain damage. The diagnosis of cryptogenic cerebral ischemia (TIA or stroke) is confirmed by a neurologist, where the symptomatic patients presented first **SC** (Braun, et al., 2004).

A0006 QUESITO: What are the consequences of the condition?¹⁷

Most clinically recognized systemic emboli involve the cerebral circulation and may result in permanent disability or death. The overall major stroke-related case fatality rate is approximately 20%, whereas the long term morbidity (permanent sequelae) occurs in approximately one fourth of patients. In these patients, several studies found that the **quality of life** associated with long-term morbidity was reduced by a factor of two or even more **R** (Nendaz, et al., 1998).

A0008 QUESITO: What is the burden of disease (mortality, disability, life years lost)?¹⁸

Stroke patients often have a reduced quality of life. One third of stroke patients reported impaired quality of life 6-12 months after his stroke, although they recovered from their neurological symptoms. Several patients do not anyways recover, so the risk of impact on both functional capacity and quality of life is evident **R** (Dellborg, et al., 2010).

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Criterion C4 – Size of population

Fonti: revisione della letteratura (statistiche nazionali e/o regionali, associazioni dei pazienti, review recenti)

Da fare:

- Riportare la prevalenza/incidenza nella nazione e/o nella regione; il numero annuale di casi (se questi dati non sono disponibili utilizzare i dati di altri paesi che possono essere comparati con quelli italiani)
- Descrivere brevemente il disegno dello studio (caratteristiche, numero di persone)

Da non fare: non includere informazioni sulla percentuale di pazienti che ricevono diversi trattamenti

SOTTOCRITERIO: Features of the technology

B0016 QUESITO: Who are the persons this technology will be used on?¹⁹

Patent foramen ovale is present in about 25,6% of the general population, according to TEE studies, and in 27,3% in autopsy studies, and can be found in up to 40% of patients with otherwise cryptogenic stroke **C** (Weimar, et al., 2009).

¹⁶ FONTI INFORMATIVE: Medical literature, at the best systematic reviews on mechanism of disease, risk factors, course, prognosis.

¹⁷ DESCRIZIONE: Qualitative description of the burden of disease for the individual (e.g. disability, pain). FONTI INFORMATIVE: Medical literature, at the best systematic reviews on mechanism of disease, risk factors, course and prognosis.

¹⁸ DESCRIZIONE: Disease-specific mortality. Prevalence of disability or disabling symptoms caused by the condition. Prevalence/Incidence of early retirement due to the condition. This question provides information on which is the most important outcome (measure) for the specific disease? INFORMATION SOURCES: Systematic reviews of epidemiological studies such as cross-sectional Studies (prevalence), cohort studies (incidence), routine statistics. Own analysis of: Disease register, administrative databases (discharge databases, reimbursement claims databases)

¹⁹ DESCRIZIONE: Define as many narrow groups as possible. The technology might behave differently in different patient groups. Are there specific populations that should not be recipients of the technology because of technical difficulties, inaccuracy or certainty of inconclusive results or because of safety issue? FONTI INFORMATIVE: Manufacturers' sites, reviews, textbooks, introduction sections of research articles, interviews.

In most clinical trials, inclusion criteria for patients undergoing transcatheter PFO closure are **SC** (Spies, et al., 2008):

- A history of unequivocal ischemic stroke documented clinically by a neurologist and radiographically by either cranial computed tomography or magnetic resonance imaging; or
- Transitory ischemic attack (TIA), defined as a transient neurological deficit or vision loss with full recovery within 24 hours confirmed clinically by a neurologist; or
- Peripheral thromboembolism verified clinically by an internist or a cardiologist, and radiographically by either computed tomography or angiography;
- platypnea-orthodeoxia syndrome or refractory hypoxemia or migraine aura;
- The exclusion of other identifiable causes for the thromboembolic event with:
 - o Ultrasound of cerebral arteries and aorta
 - o 24-hour Holter-electrocardiography
 - o 24-hour blood pressure measurements
 - o The presence of a PFO with or without ASA with spontaneous or inducible right-to-left shunting during contrast transesophageal echocardiography or transthoracically, if clearly visible. A small shunt volume is defined as 3-20 bubbles, and a large shunt volume as > 20 bubbles passing the PFO into the left atrium.

On the other hand, exclusion criteria for PFO closure are:

- Atrial fibrillation;
- Significant stenosis of the carotid arteries;
- Known thrombophilic disorders;
- Pregnancy;
- Recent myocardial infarction (MI);
- Prosthetic heart valve;
- Mitral stenosis;
- Endocarditis;
- Cardiac myxoma;
- Severe atherosclerosis or dissection of the aorta;
- Intracranial vascular disease;
- Previous intracranial hemorrhage;
- Vasculitis;
- Acute infection;
- Allergic reaction to medication necessary during or after the procedure, such as clopidogrel, aspirin and nickel.

Migraine

The inclusion criteria of the recent MIST trial, which is the only randomized controlled trial completed at the moment, included **RCT** (Dowson, et al., 2008) **SC** (Rigatelli, et al., 2010):

- Minimum 1-year history;
- 5 or more days of migraine/month;
- Aura;
- Symptoms refractory to 2 preventative medications;
- Moderate-to-large PFO assessed only by TEE;
- Maintenance of prophylactic medications.

Patients with coagulation abnormalities or with a **serious risk of paradoxical embolization** were **excluded**.

SOTTOCRITERIO: Target Condition

A0007 QUESITO: How many people belong at the moment (will belong) to the specific target group (describe according to sex, age)?²⁰

Prevalence of PFO has no particular difference between men and women (men 26,8%, women 27,7%), however it decreases with age (34% in aged 1-29 years; 25% in 30-79 years; 20% in 80 years or more), and in

²⁰ DESCRIZIONE: Incidence and/or prevalence of the target condition or the indication for use of the technology

FONTI INFORMATIVE: Systematic reviews of epidemiological studies such as cross-sectional Studies (prevalence), cohort studies (incidence), routine statistics. Own analysis of: Disease register, administrative databases (discharge databases, reimbursement claims databases)

most individuals, it will remain asymptomatic for life. Most series of PFO closure evaluated younger patients, however little is known about the recurrence rate of thromboembolic events (TEs) in patients over the age of 55 years undergoing PFO closure following cryptogenic TEs thus the attention to this patient group is increasing **R** (Meier, et al., 2012).

In the European population, the annual incidence of a first ischemic stroke is 139 per 100.000 inhabitants. Since around 60% of these events can be attributed to conventional causes, the annual risk attributed to paradoxical embolism has been estimated at 28 per 100.000 persons with PFO per year. The association of PFO with cryptogenic stroke has been repeatedly confirmed. More recently, this observation has been extended to adults > 55 years, with a significantly higher prevalence of PFO alone (28,3 vs. 11,9%; OR 2,9; 95% CI 1,7–5,0; $P < 0,001$) as well as of PFO associated with ASA (15,2 vs. 4,4%; OR 3,9; 95% CI 1,8–8,5; $P < 0,001$) among patients with cryptogenic stroke compared with those with conventional stroke causes **E** (Handke, et al., 2007).

In the US, 700.000 strokes happen every year, of which 75% are ischemic and approximately 140.000 are cryptogenic. By extrapolation, 70.000 of cryptogenic strokes may be associated with PFO and may benefit from device closure of this defect, since the risk of developing a stroke in someone with the PFO is 1 in 1.000/year. The recurrence rate in patients with a PFO who have already suffered a stroke is approximately 2% annually, while higher stroke rates (15%) have been associated with the presence of an atrial septal aneurysm (ASA) **R** (Bailey, et al., 2004).

A report from the Swedish HTA-centrum of the Sahlgrenska Universitetssjukhuset depicts the situation in Sweden:

In Sweden live 100 000 individuals with previous stroke, which corresponds to approximately 16 000 individuals in the region of VästraGötaland (VGR). Approximately 25% of all strokes at younger ages are cryptogenic, which is also reported in a recent western Swedish study, SAHLIS of Jood and colleagues (2005). That means about 4,000 individuals with completion of cryptogenic stroke in VGR. According to the national registry of stroke victims, about 30,000 individuals are for stroke and 8000 for TIA for each year in Sweden. This means that each year 5,000 patients suffering from stroke in VGR, one fifth of patients stroke victims are under 65 years, equivalent to 1000 young stroke episodes of VGR / year. Ischemic stroke is 85% of all strokes, ie, 850 ischemic strokes / year in VGR. In the age group under 65 are cryptogenic stroke 25% of all ischemic stroke as the VGR is likely that about 210 patients under 65 years diagnosed annually with cryptogenic stroke. Of these patients, 25-50% has also a PFO, so about 100 patients a year from VGR could be considered for the presented treatment **R** (Dellborg, et al., 2010).

Regarding specific information on the Lombardy Region, an exploratory analysis of the Regional Data Warehouse on patients who underwent the PFO closure procedure, from years 2003 to 2011, showed a total of 6671 patients, of which 2071 non residents and 4600 residents, with an average of about 740 patients/year (with a peak of 918 hospitalizations in 2008). An age stratification highlights a majority of cases aged 41-60 (41,37%), followed by 19-40 patients (26,01%).

Furthermore, throughout 9 years, patients with stroke/TIA who didn't undergo PFO closure were 187.322, while patients with closure procedure, independently from stroke/TIA event, were 4001; of these, 2487 patients didn't have any previous event, and 365 were the possible cryptogenic stroke ones, without any other disease, undergoing PFO closure. Anyways, with a more extensive criterion, other 1052 further cases could be potentially characterized as cryptogenic, when considering that the cerebral occlusion codification didn't exclude the diagnosis of a cryptogenic stroke. The correspondent potential cryptogenic strokes not subjected to PFO closure are respectively 49.340 and 60.743, as represented in the table below. In the first column, the absence (0) or presence (1) of single criteria are reported: PFO closure procedure (PFO), stroke/TIA event (ictustia), atrial fibrillation (FA), cerebral bleeding (emo), pre-cerebral arteries occlusion (occlu433), cerebral arteries occlusion (occlu434), and carotid unblocking (caro) E (Barbieri, 2012).

pfo	ictustia	fa	emo	occlu433	occlu434	caro	Frequency	Percent	Frequency	Percent
0	1	0	0	0	0	0	49340	25.79	49340	25.79
0	1	0	0	0	0	1	21598	11.28	70930	37.07
0	1	0	0	0	1	0	60743	31.75	131673	68.82
0	1	0	0	0	1	1	1506	0.79	133179	69.61
0	1	0	0	1	0	0	4461	2.33	137640	71.94
0	1	0	0	1	0	1	2705	1.41	140345	73.35
0	1	0	0	1	1	0	3489	1.82	143834	75.18
0	1	0	0	1	1	1	1065	0.56	144899	75.73
0	1	0	1	0	0	0	1157	0.60	146056	76.34
0	1	0	1	0	0	1	265	0.14	146321	76.48
0	1	0	1	0	1	0	1777	0.93	148098	77.41
0	1	0	1	0	1	1	66	0.03	148164	77.44
0	1	0	1	1	0	0	134	0.07	148298	77.51
0	1	0	1	1	0	1	65	0.03	148363	77.54
0	1	0	1	1	1	0	121	0.06	148484	77.61
0	1	0	1	1	1	1	36	0.02	148520	77.63
0	1	1	0	0	0	0	10576	5.53	159096	83.15
0	1	1	0	0	0	1	2321	1.21	161417	84.37
0	1	1	0	0	1	0	21796	11.39	183213	95.76
0	1	1	0	0	1	1	275	0.14	183488	95.90
0	1	1	0	1	0	0	903	0.47	184391	96.38
0	1	1	0	1	0	1	348	0.18	184739	96.56
0	1	1	0	1	1	0	941	0.49	185680	97.05
0	1	1	0	1	1	1	155	0.08	185835	97.13
0	1	1	1	0	0	0	372	0.19	186207	97.32
0	1	1	1	0	0	1	47	0.02	186254	97.35
0	1	1	1	0	1	0	951	0.50	187205	97.85
0	1	1	1	0	1	1	25	0.01	187230	97.86
0	1	1	1	1	0	0	29	0.02	187259	97.87
0	1	1	1	1	0	1	7	0.00	187266	97.88
0	1	1	1	1	1	0	46	0.02	187312	97.90
0	1	1	1	1	1	1	10	0.01	187322	97.91
1	0	0	0	0	0	0	2487	1.30	189809	99.21
1	1	0	0	0	0	0	365	0.19	190174	99.40
1	1	0	0	0	0	1	4	0.00	190178	99.40
1	1	0	0	0	1	0	1052	0.55	191230	99.95
1	1	0	0	0	1	1	6	0.00	191236	99.95
1	1	0	0	1	0	0	19	0.01	191255	99.96
1	1	0	0	1	1	0	14	0.01	191269	99.97
1	1	0	0	1	1	1	1	0.00	191270	99.97
1	1	0	1	0	0	0	2	0.00	191272	99.97
1	1	0	1	0	1	0	6	0.00	191278	99.97
1	1	0	1	0	1	1	1	0.00	191279	99.98
1	1	1	0	0	0	0	12	0.01	191291	99.98
1	1	1	0	0	1	0	32	0.02	191323	100.00

Table 1 - Patients subgroups and related frequencies

Migraine

Regarding migraine, it is a common recurrent and disabling headache disorder affecting at least 10% of population, with a 3:1 female preponderance (its prevalence is 18% in women and 6% in men). A typical migraineur has one to two attacks per month, with a median duration of 24 h. Around one third of migraineurs have migraine with aura. Commonly used preventive medications such as propranolol, amitriptyline or anticonvulsants reduce headache frequency in the range of 30-50%, as compared to placebo.

Numerous studies show that prevalence of migraine in PFO patients is 2-5 times higher than the prevalence in patients without PFO, however information provided by the NOMAS (Northern Manhattan Study) on a multiethnic population of 1101 patients point out that the prevalence of PFO is not significantly different in individuals with migraine (with or without aura) compared to individuals without migraine (PFO+migraine 26/178, 14,6%; PFO without migraine 138/923, 15,0%; $p=0,9$). Approximately half of migraineurs with aura have PFO E (Di Tullio, et al., 2007).

Criterion C5 – General Healthcare Goals (prevention, risk reduction)

Fonti: revisione della letteratura.

Da fare:

- Riportare la riduzione del rischio attesa con un intervento preventivo
- Fornire informazioni per identificare se il beneficio offerto dalla tecnologia possa servire alla sanità pubblica, ad es. a livello della popolazione (riduzione della mortalità, della trasmissione della malattia)

Da non fare: non comparare la tecnologia esaminata con i competitori

SOTTOCRITERIO: Utilisation

A0011 QUESITO: How much is the technology being used?²¹

Data about the diffusion of PFO closure devices are difficult to find, however a multicenter survey on 18 PFO closure centers in Europe and United States infers an approximation of 8.000 PFO closure procedures performed each year in the United States, with various devices: even though currently there is no US Food and Drug Administration approval for PFO closure indication, PFO are being closed off-label without a clear understanding of the relative frequency of complications.

There were 13.736 devices implanted among the 18 centers over the past 3 to 9 years, of which the most utilized were: Amplatzer (66%), CardioSEAL (15%), and Helex (10%). The figure below shows the level of diffusion and the location for each one of them R (Verma, et al., 2011).

Institution	Implantations				Total
	AMP	CS	HX	Other	
Brescia, Italy	750	0	0	110	860
Columbia University	4	1,104	73	2	1,183
Emory University	225	0	5	20	250
Evanston Hospital	42	0	53	3	98
Intermountain Medical Center, SLC	1,529	246	250	0	2,025
Mayo Clinic, Rochester	660	3	32	0	695
Rush University	600	0	150	0	750
Sankt Katharinen, Frankfurt, Germany	1,635	27	485	1,128	3,275
Swedish Medical Center	35	211	0	0	246
UCLA	150	35	45	0	230
UMDNJ, Cooper University Hospital	125	40	0	0	165
University Hospital, Bern, Switzerland	1,350	20	5	125	1,500
University of Colorado	425	25	0	0	450
University of Milan, Italy	348	0	0	15	363
University of Pennsylvania	115	105	5	0	225
University of Utah	484	35	91	0	610
University of Washington	92	112	7	0	211
Washington University, St. Louis	540	60	0	0	600
Total	9,109	2,023	1,201	1,403	13,736

Figure 1 - Device implantations by institution: AMP = Amplatzer; CS = CardioSEAL; HX = Helex; SLC = Salt Lake City; UCLA = University of California at Los Angeles; UMDNJ = University of Medicine and Dentistry of New Jersey

SOTTOCRITERIO: Change-in management

D0010 QUESITO: How does the technology modify the need for hospitalization?²²

A long term observational study, which followed up prospectively for up to 15 years 308 consecutive patients with cerebrovascular events presumably related to PFO, compared outcomes of those who underwent percutaneous PFO closure (150 patients) and those with medical treatment (158 patients). The primary outcome was a composite of stroke, transient ischemic attack, or peripheral embolism.

At a median follow up of 9 years, with an overall procedural success of 99%, the primary composite outcome occurred in 11 patients slated to PFO closure (11%) and 22 patients slated to medical treatment (21%; hazard

²¹ FONTI INFORMATIVE: Utilisation reviews, audits, studies on praxis-variation. Own primary analysis of: Disease register, procedure register, device register, administrative data (DRG, discharge databases, reimbursement claims database).

²² DESCRIZIONE: Use of technology may have an impact on morbidity related to the need for hospitalizations. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

ratio = 0,43; 95% confidence interval = 0,20-0,94; P = 0,33), requiring hospitalization. The treatment effect was driven by a decrease in the risk of transient ischemic attack of 5% versus 14%, respectively (hazard ratio = 0,31; 95% confidence interval = 0,10-0,94; P = 0,039). The risk of all-cause (6% in both groups) and cardiovascular (3% in both groups) mortality appeared to be identical.

The major strength of this study is the long follow up of > 10 years. Included patients were among the first to receive percutaneous PFO closure, as they had been enrolled between 1994 and 2000. Therefore, the study has the longest follow up duration available to date, providing robust long-term data on both the effectiveness and safety of percutaneous PFO closure. However, results may be subject to confounding by indication owing to the lack of randomization **C** (Wahl, et al., 2012).

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Criterion C6 – Description of technology and benefits areas (care, symptomatic relief, etc.)

Fonti: revisione della letteratura

Da fare: fornire informazioni per identificare le aree di beneficio offerto dalla tecnologia per il paziente (ad es. cura; prolungamento della vita; sollievo sintomatico; ecc.)

Da non fare: non comparare la tecnologia esaminata con i competitori

TECHNOLOGY DESCRIPTION

SOTTOCRITERIO: Features of the technology

B0001 QUESITO: What is this technology?²³

Devices for percutaneous closure of the PFO are introduced via femoral vein through a catheter into the heart and across the patent foramen ovale: the closure device is then inserted through the defect thanks to the delivery sheath and released, thus closing the foramen ovale **G** (NICE, 2005).

The occluder usually consists of two parallel discs of different diameters resembling umbrellas, which are connected by an articulating center post, allowing independent orientation of the left and right atrial umbrella. A fine-wire braided Nitinol mesh (NDC), which is contained into the device, is intended to stimulate the body's natural adhesion response for permanent closure of the PFO, and it also provides an immediate barrier to the conduction of emboli before permanent closure **SC** (Zimmermann, et al., 2010).

Examples and specific features of devices are the following:

Device name	Manufacturer	Sizes	Features
Amplatzer	AGA Medical, Golden Valley, MN, USA	18/25/35 mm	It is a self-expanding Nitinol wire mesh with a right atrial disc and a much smaller atrial disc with a connector; the Nitinol device has the ability to adopt the shape of the septum SC (Bissessor, et al., 2011).
Premere	St. Jude Medical, Maple Grove, MN, USA	25 mm	It is designed to close small PFO of variable size and length with right and left anchor arms connected by an adjustable flexible tether to suit the PFO anatomy SC (Bissessor, et al., 2011).
SeptRx	SeptRx, Inc., Fremont, California, USA	14 mm	It consists in a laser-cut, electropolished, self expanding Nitinol frame with flexible anchor struts at the top of the device, which uncoil from their curved shape to adapt to a variety of PFO tunnel lengths SC (Zimmermann, et al., 2010).
CardioSEAL	NMT Medical, Boston, Massachusetts, USA	28/33 mm	It is constructed from a low-profile nickel-cobalt alloy framework shaped like an umbrella to which a knitted polyester fabric is attached R (Homma, et al., 2005).
STARFlex	NMT Medical, Boston, Massachusetts, USA		It is a double umbrella with a 4-arm metallic framework SC (Fischer, et al., 2008).

²³ DESCRIZIONE: Provide a short technical description: Type of device, operation, imaging, etc. Biological rationale and mechanism of action of the technology. FONTI INFORMATIVE: Manufacturer, effectiveness studies, clinical experts, studies in basic science, textbooks.

Intrasept	Cardia, Eagan, MN, USA	20/25/30/35 mm	It consists in two discs made of Ivalon (polyvinyl alcohol), and each umbrella is expanded by a six Nitinol arms SC (Spies, et al., 2008).
Occlutech Figulla	Occlutech GmbH, Jena, Germany	23x25 mm/ 27x30 mm	It consists in a Nitinol wire mesh to create a smooth and flexible outer layer. Two retention discs allow for a central pin on the right atria side and are connected by a 3 mm waist in the center. Two polyethylene terephthalate (PET) patches assure complete closure after impantation SC (Krizanic, et al., 2010).
Sideris buttoned	Custom Medical Devices, Amarillo, TX, USA	NR	NR (not reported)
Angel Wings	Microvena Corp., White Bear Lake, MN, USA	NR	NR
PFO STAR	Cardia, Eagan, MN, USA	NR	NR
Helex	W.L. Gore and Associates, Inc, Flagstaff, Arizona, USA	NR	NR
ASDOS, Premere, Biostar, GoreHelex, Clamshell, Cardia			

Table 2 - Table of comparison of different PFO closure devices

B0002 QUESITO: Why is this technology used?²⁴

Possible treatment modalities to prevent recurrent events among stroke patients with a PFO include medical treatment with warfarin or antiplatelet agents, percutaneous PFO closure, and surgical PFO closure. Factors associated with paradoxical embolization are, in fact, size of PFO, ASA, Eustachian Valve and Chiari's Network, and venous thrombus and hypercoagulable state.

Large PFOs are demonstrated to be significantly more prevalent among cryptogenic stroke patients, compared with those with known cause of stroke. Thereafter, the prevalence of ASA, is greater among patients with embolic events, additionally the PFOs seen in the presence of ASA tend to be large compared with those seen without associated ASA. Lastly, the Eustachian Valve among adults can cause a significant right-to-left shunt in the presence of an interatrial communication by altering the blood flow pattern; the presence of Chiari's Network and filamentous strands in the right atrium is also associated with the presence of PFO. Therefore, the presence of atrial anatomic variants that can promote flow from the inferior vena cava toward the PFO may increase the chance of paradoxical embolization beyond that associated with PFO size.

Thus, in order to avoid these events to incur, and to prevent major bleeding resulting from medical therapy, especially from the use of warfarin, closure of PFO started to spread among management techniques. With the advent of percutaneous closure devices, the surgical approach is no longer widely used.

Percutaneous closure has been shown in some clinical studies to give lower event rates compared with medical therapy ($P<0,0001$), however, very importantly, indirect comparison of medical treatment and percutaneous closure is difficult to interpret, due to patients' selection bias and to not uniform inclusion criteria for the studies **R** (Homma, et al., 2005).

B0005 QUESITO: What is the place and context for utilising the technology?²⁵

Younger patients with cryptogenic stroke are investigated and dealt with in the acute phase of profiled special unit, stroke unit, in neurology and internal medicine. Depending on residual symptoms and function, their action is the recent rehabilitation of the varying degrees on an outpatient basis and patients are often managed initially on specialty outpatient clinic, and later in primary care.

²⁴ DESCRIZIONE: Describe the aim of using the technology: How is it expected to be an improvement as compared to previous technologies used for the same health problem? FONTI INFORMATIVE: Manufacturer, effectiveness studies, clinical experts.

²⁵ DESCRIZIONE: At which level(s) of health care (self-care, primary, secondary, tertiary) will the technology be used? FONTI INFORMATIVE: Manufacturer, effectiveness studies, clinical experts, legislation. National or local judgement.

In Italy, the intervention is normally implemented in many centers, especially in Lombardy region. As a percutaneous procedure via femoral vein, it is usually practiced in hemodynamic/angiography room or in the cardiac catheterization laboratory, at neonatal, adult and ageing levels (Lombardy Region, 2011).

B0006 QUESITO: Are there any special features relevant to this technology?²⁶

B0004 QUESITO: Who will apply this technology?²⁷

The procedure should be done by an interventional cardiologist and supporting team with specific training in the procedure **G** (NICE, 2010).

B0003 QUESITO: Phase of the technology: When was it developed or introduced in health care?²⁸

Initial techniques of percutaneous atrial septal defect closure were documented in the 1970s and the first suggestion that PFO closure would reduce the incidence of recurrent strokes was demonstrated by Bridges et al. in 1992. In that case, in a group of 36 patients who underwent PFO closure with the Clamshell septal umbrella, no serious complications occurred. Specifically, there were no strokes, no episodes of hemodynamic instability, and no infectious complications. A brachial plexus injury, probably related to positioning during the catheterization, occurred in one patient, with subsequent full recovery.

By echocardiographic color flow mapping, closure of the patent foramen ovale was complete in 28 patients (82%), five had tiny (, 1 mm) leaks (four predominantly right to left and one left to right), and one patient had a 2-3-mm right-to-left leak. The latter patient had a transient focal neurological deficit (amaurosis fugax) 1 month after the procedure. Three patients with complete closure of the atrial defect had transient events, and no patient had a stroke, brain abscess, systemic arterial embolism, or bacterial endocarditis after closure of the atrial defect, during a total surveillance period of 242 patient-months in the preclosure period and 221 months in the postclosure period **R** (Bridges, et al., 1992).

SOTTOCRITERIO: Ownership & liability

I0021 QUESITO: What are the width, depth and length of the manufacturers guarantee?²⁹

I0022 QUESITO: Is the user guide of the technology comprehensive enough?³⁰

SOTTOCRITERIO: Life-Cycle

A0019 QUESITO: In which phase is the development of the technology (experimental, emerging, routine use, obsolete)?³¹

B0017 QUESITO: Is the technology rapidly changing / improving?³²

²⁶ DESCRIZIONE: Any points where this technology is different from its predecessors (other technologies used for similar purposes); new aspects that need to be considered when applying it. FONTI INFORMATIVE: Manufacturer, effectiveness studies, clinical experts.

²⁷ DESCRIZIONE: What types of professionals (nurses, doctors, other professionals) or patients (all with a certain disease, narrowly defined groups) will be using this technology? FONTI INFORMATIVE: Manufacturer, effectiveness studies, clinical experts, legislation. National or local judgement.

²⁸ DESCRIZIONE: Is it a truly novel one, or has it been used earlier for this or some other purpose? Is the technology fully developed or in its early stages? Most technologies will be introduced at approximately the same time in several countries. If an HTA has been done more than a few months before using it, the technology might have been studied in more detail and moved into another phase (with more published trials, for example). FONTI INFORMATIVE: Manufacturer, effectiveness studies.

²⁹ DESCRIZIONE: The terms of the manufacturers guarantee are of importance to the health care unit as well as to the society's health care sector when considering whether it is economically and/or liabilitywise advantageous to introduce the technology or not. FONTI INFORMATIVE: Manufacturer.

³⁰ DESCRIZIONE: The wording and clarity of the user guide of the technology can have legal effects on the liability issue in case the technology is not working as expected. FONTI INFORMATIVE: Manufacturer.

³¹ DESCRIZIONE: This is related to the question whether there is enough evidence or experiences on the use of the technology on the condition. FONTI INFORMATIVE: Literature. Horizon scanning databases, ongoing research databases. Information from manufacturers.

SOTTOCRITERIO: Other**A0022 QUESITO: Who manufactures the technology?**

The main manufacturers of PFO closure devices and the related device names are listed below:

Device name	Manufacturer
Amplatzer	AGA Medical, Golden Valley, MN, USA
Premere	St. Jude Medical, Maple Grove, MN, USA
SeptRx	SeptRx, Inc., Fremont, California, USA
CardioSEAL	NMT Medical, Boston, Massachusetts, USA
STARFlex	NMT Medical, Boston, Massachusetts, USA
Intrasept	Cardia, Eagan, MN, USA
Occlutech Figulla	Occlutech GmbH, Jena, Germany
Sideris buttoned	Custom Medical Devices, Amarillo, TX, USA
Angel Wings	Microvena Corp., White Bear Lake, MN, USA
PFO STAR	Cardia, Eagan, MN, USA
Helix	W.L. Gore and Associates, Inc, Flagstaff, Arizona, USA

Table 3 - Different closure devices and related manufacturers

See QUESITO B0001

BENEFITS AREAS**SOTTOCRITERIO: Target Condition**

A0009 QUESITO: What aspects of the burden of disease are targeted by the technology, i.e. are expected to be reduced by the technology?³³

SOTTOCRITERIO: Function / HRQL (Health-related quality of life)

D0011 QUESITO: What is the effect of the intervention on global improvement of function?³⁴

D0012 QUESITO: What is the effect of the technology on health-related quality of life?³⁵

D0013 QUESITO: What is the effect of the intervention on disease specific quality of life?³⁶

D0014 QUESITO: What is the effect of the intervention on return to work?³⁷

³² DESCRIZIONE: For end users it is useful to know if a new improved technology is expected in the near future. FONTI INFORMATIVE: Manufacturers' sites, reviews, textbooks, introduction sections of research articles.

³³ DESCRIZIONE: The application of the technology may target only one aspect of the burden of disease, eg. disability but not mortality. Or mortality but not symptomatology. FONTI INFORMATIVE: Systematic reviews of epidemiological studies such as cross-sectional Studies (prevalence), cohort studies (incidence), routine statistics. Own analysis of: Disease register, administrative databases (discharge databases, reimbursement claims databases).

³⁴ DESCRIZIONE: Use of technology may have an impact on functional ability
FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

³⁵ DESCRIZIONE: Use of technology may have an impact on quality of life
FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

³⁶ DESCRIZIONE: Use of technology may have an impact on quality of life
FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

³⁷ DESCRIZIONE: Use of technology may have an impact on working ability.
FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

D0015 QUESITO: What is the effect of the intervention on return to previous living conditions?³⁸

D0016 QUESITO: How does the use of technology affect activities of daily living?³⁹

³⁸ DESCRIZIONE: Use of technology may have an impact on ability to return to previous living conditions.

FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

³⁹ DESCRIZIONE: Use of technology may have an impact on ability to perform daily activities.

FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

Dimension D2: Safety

Criterion C7 – Improvement of Safety and Tolerability

Fonti: revisione della letteratura (pubblicazioni, monografia del prodotto, dati tecnici, database di sorveglianza)

Da fare:

- Riportare eventi avversi in formato tabellare (tutte le cause dovute al trattamento) per intervento e comparatori chiave nella popolazione target; specificare la durata del follow up e le dimensioni della popolazione
- Se la lista degli eventi avversi è troppo lunga, riportare solo quelli con un tasso di incidenza CUT-OFF (riportare il cut-off usato)
- Riportare tutti gli eventi avversi seri e le morti
- Riportare le interruzioni dovute ad eventi avversi
- Riportare i pericoli dovuti alla tecnologia e ai comparatori

SOTTOCRITERIO: Mortality / Morbidity

D0008 QUESITO: What is the mortality and morbidity related to the intervention?

The mortality rate due to this intervention has demonstrated in many observational studies to be low: according to a long-term observational study by C (Wahl, et al., 2012), where 206 consecutive patients with cerebrovascular events presumably related to PFO underwent either percutaneous PFO closure (103 patients) or medical treatment (103 patients), with a mean follow up of 10 years, the overall mortality rate resulted around the 6% for both the PFO closure and the medical treatment group (HR [95% CI] 1,00 (0,32-3,10), P 1,00), thus 0,6% every year.

D0004 QUESITO: What is the mortality related to the technology studied?⁴⁰

See QUESITO D0008

SOTTOCRITERIO: Patient safety

C0001 QUESITO: What kind of harms can use of the technology cause to the patient and what is the incidence, severity and duration of harms?⁴¹

Since its first introduction in the early 1990s, percutaneous PFO closure has been shown safe and feasible in numerous studies, even in older patients (i.e. with age > 55 years) using a variety of devices. The reported success rates varied between 90 and 100%, with complication rates between 0 and 10%. Complete PFO closure was reported in 51–100% of patients, and yearly recurrence rates of ischaemic strokes and TIAs varied between 0 and 3,4%.

However, unlike medical therapy, many complications are related to the transcatheter device closure, which have been reported in numerous observational studies. The major complication rate ranges between 0,2% and 1,5% for procedural-related death, hemorrhage requiring transfusion, cardiac tamponade, need for surgical intervention and fatal pulmonary emboli. Minor complications including bleeding not requiring transfusion, periprocedural atrial arrhythmias, transient atrioventricular node block, device arm fractures, device embolization, thrombosis, arteriovenous fistula formation and femoral hematomas range from 7,9% to 11,5% R (Khairy, et al., 2003) SC (Spies, et al., 2008).

Newer percutaneous devices and smaller catheters have led to a decrease in reported major and minor complications.

The incidence of atrial fibrillation after device closure of a PFO is estimated to be 2,5% annually, but this depends on the device used R (Tobis, et al., 2012).

Thrombosis of the device is reported in between 0 to 4% at a follow-up 6-26 months. It is worth noting that the devices in use today have a low risk of thrombosis, 0 to 0,3% at a follow-up of one to two years.

⁴⁰ DESCRIZIONE: Use of technology may have an impact on mortality related to the intervention studied. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data.

⁴¹ DESCRIZIONE: Are the harms intrinsic to the technology (primary effect) or application dependant (secondary effects) or an unrelated event consequent on its use? FONTI INFORMATIVE: Observational research, safety monitoring databases, registers, statistics.

More specifically in CLOSURE I, the only one randomized controlled trial available at the moment, of the patients who were randomly assigned to treatment, 402 underwent attempted implantation of the STARFlex closure device and 458 received medical therapy; all these patients were included in the safety analysis. There were no significant differences in the rates of serious adverse events between the two groups, although the types of serious adverse events did differ. Protocol-specified major vascular procedural complications occurred only in the closure group, with a rate of 3,2% (13 patients). Atrial fibrillation was significantly more frequent in the closure group than in the medical-therapy group (23 patients [5,7%] vs. 3 patients [0,7%], $P<0,001$), as listed in the figure below. Atrial fibrillation occurred within 30 days after the implantation procedure in 14 of 23 patients (61%); it was transient in 17 patients and persistent in 6 patients **RCT** (Furlan, et al., 2012).

Event	Closure (N=402)	Medical Therapy (N=458)	P Value
Major vascular procedural complication — no. (%)†	13 (3.2)	0	<0.001
Atrial fibrillation — no. (%)	23 (5.7)‡	3 (0.7)	<0.001
Major bleeding episode — no./total no. (%)§	10/378 (2.6)	4/374 (1.1)	0.11
Death other than end point — no. (%)	2 (0.5)¶	4 (0.9)	0.51
Nervous system disorder — no. (%)**	6 (1.5)	16 (3.5)	0.15

Figure 2 - Serious adverse events in CLOSURE I trial

Differences in reporting of adverse events between observational studies and the CLOSURE I trial did not allow direct comparisons of the various types of adverse events between study designs. Overall, it was evident that atrial fibrillation and major vascular complications were much more common events in CLOSURE I compared to the observational studies **R** (Kitsios, et al., 2012).

The table in the following page summarizes the main adverse events of transcatheter PFO closure described in 20 clinical studies, both comparative and single arm, and in the Closure I.

Surgical removal

There have been isolated reports of patients who needed to have their device removed, which implied open heart surgery in order to extract the PFO device.

A multicenter survey examining 18 PFO closure centers in Europe and the United States registered 13.736 devices implanted over the past 3 to 9 years, of which 38 (0,28%) were explanted at these institutions. Among the 38 total explantations, 14 (37%) patients underwent surgical excision of their device for chest pain, and of these, 7 (18%) had nickel allergy, 12 (32%) devices were explanted because of the persistence of a residual shunt; 4 (11%) patients had the device removed secondary to thrombus formation on the device, and 2 (5%) devices were taken out because of pericardial effusion. Erosion was responsible for 2 (5%) devices being explanted. Recurrent stroke accounted for the removal of 1 (3%) PFO closure device, 1 (3%) device was excised secondary to development of an infection stemming from the device, and 1 (3%) was removed due to the persistence of migraine symptoms. There was 1 (3%) device taken out due to an unspecified cause. In addition to the 38 patients who underwent explantation, there were 3 patients with prolonged chest pain (>1 year) who did not undergo surgical excision of their device, but surgery was discussed with the patient. In 1 patient, the symptoms resolved gradually after 1 year, and another patient was lost to follow-up. The frequency of removal seemed to be device-dependent: however, patients should be made aware of the possibility of device explantation when informed consent is obtained **R** (Verma, et al., 2011).

Migraine

A transient and paradoxical increase in migraine headaches in a minority of patients immediately after percutaneous PFO or ASD closure is well-documented. This has been attributed to enhanced inflammation induced by the device, especially if the recipient has a nickel allergy, which affects 15% of the general population. A local inflammatory reaction on the LA (Left Atrium) side might lead to platelet activation and release of serotonin or other potential chemical triggers of migraine. This hypothesis is supported by the observation that clopidogrel or steroids often reduce the post-procedural migraines. In addition, these patients might also experience chest discomfort and palpitations, presumably due to local inflammation, nickel sensitivity, or formation of fibrous scar tissue. These side effects might take 3 to 6 months to resolve but on occasion might be so severe that the patient requests removal of the device **R** (Tobis, et al., 2012).

The only completed randomized trial of PFO closure for migraine headaches is the MIST (Migraine Intervention with STARFlex Technology) Trial. 147 patients were enrolled and randomized 1:1 to device closure with the STARFlex septal implant or a sham procedure consisting of a skin incision in the groin under general anesthesia. The procedural complications were 6,8% in the MIST I trial, which is higher than that reported in multiple observational studies **RCT** (Dowson, et al., 2008).

C0007 QUESITO: What are the special features in using (applying/interpreting/maintaining) the technology that may increase the risk of patient safety?⁴²

As shown in some reviews and clinical trials, the rate of major complications occurring with transcatheter closure of patent foramen ovale is less than 2%, moreover recent reports suggest that adverse events with older devices may in part reflect a learning curve and that newer devices pose less risk of dislodgment and embolization, and offer a higher rate of complete closure **R** (Khairy, et al., 2003).

C0002 QUESITO: What is the dose relatedness of the harms to patients?⁴³

C0003 QUESITO: What is the timing of onset of harms to patients: immediate, early or late?⁴⁴

Adverse events may be acute (related to the device implant procedure) or late (related to the proper positioning of the device, to its complete endothelialization and interaction between device and heart structures). Late complications increase also during follow up **SC** (Krumdordf, et al., 2004).

See QUESITO C0008

C0004 QUESITO: Is the incidence of the harms to patients likely to change over time?⁴⁵

C0005 QUESITO: Are there susceptible patient groups that are more likely to be harmed through use of the technology?⁴⁶

Exclusion criteria for transcatheter PFO closure are for patients with **SC** (Spies, et al., 2008):

- Atrial fibrillation;
- Significant stenosis of the carotid arteries;
- Known thrombophilic disorders;
- Pregnancy;
- Recent myocardial infarction (MI);
- Prosthetic heart valve;
- Mitral stenosis;
- Endocarditis;
- Cardiac myxoma;
- Severe atherosclerosis or dissection of the aorta;
- Intracranial vascular disease;
- Previous intracranial hemorrhage;
- Vasculitis;
- Acute infection;
- Allergic reaction to medication necessary during or after the procedure, such as clopidogrel, aspirin and nickel.

C0008 QUESITO: What is the safety of the technology in comparison to alternative technologies used for the same purpose?⁴⁷

⁴² DESCRIZIONE: Is there evidence for operator dependent harms? Is there a learning curve and what is its consequence? Is there is a big intra- or inter-observer variation in the reading of test results, what is its consequence? FONTI INFORMATIVE: Research articles, manufacturers' product data sheets, safety monitoring databases

⁴³ DESCRIZIONE: Here one should consider also the accumulated harm due to repeated testing. FONTI INFORMATIVE: Research articles, manufacturers' product data sheets, safety monitoring databases.

⁴⁴ DESCRIZIONE: The onset of the harm will be different dependant on the mechanism of action and type of technology. Some harms may not be detected because the duration of follow up is not sufficiently long. FONTI INFORMATIVE: Manufacturers/ medical literature/ grey literature/ registries/ national or international safety monitoring systems.

⁴⁵ DESCRIZIONE: For some technologies the occurrence of harms may change over time and be dependant on the experience or training of the operator? FONTI INFORMATIVE: Medical literature/ grey literature/ professional societies/ registries.

⁴⁶ FONTI INFORMATIVE: Research articles.

The optimal management of PFO patients remains controversial. Long-term anticoagulation or antiplatelet therapy, surgical PFO closure, and percutaneous transcatheter closure of the PFO have been proposed as therapeutic options. Medical therapy and surgical closure are associated with a significant morbidity and mixed results regarding stroke prevention. Transcatheter closure of PFO offers the advantages of closure of the defect without the disadvantages of open-heart surgery, since it is a minimally invasive procedure which can be performed with high success and low morbidity. With respect to secondary prevention of recurrent embolic events, percutaneous PFO closure appears to be clinically at least as effective as medical treatment **R** (Meier, et al., 2012).

Regarding medical therapy, the results of CLOSURE I underline higher adverse event rates related to death and nervous system disorder (respectively 0,9% vs 0,5% closure group and 3,5% vs 1,5% closure group).

In other comparative studies the risk underlined with medical therapy is for higher major bleeding, compared to percutaneous closure, furthermore warfarin is considered to be better than antiplatelet and comparable to surgical closure in terms of recurrence rate of neurological events.

However, the mortality and morbidity risks from surgery are immediate at the time of therapy **SM** (Homma, et al., 2002).

Adverse events incurring after percutaneous PFO closure are device-related, since in different clinical trials some of them resulted to be less safe than others. In a randomized trial comparing 3 transcatheter PFO devices (CardioSEAL-STARFlex occluder, Amplatzer PFO/ASD occluder, and Gore Helex occluder), the STARFlex device had a 3,6% incidence of thrombus formation at 30-day follow-up, compared with 0% for the other 2 devices. Procedural complications have also been significantly higher for the STARFlex device, including a higher rate of peri-procedural atrial fibrillation (5% vs. 1,3% for the Amplatzer and 0,9% for the Gore Helex). There was also a high rate of large residual shunt (13%) with this device. These negative aspects of the STARFlex device might have contributed to the higher-than-expected recurrent stroke rate in the CLOSURE I trial.

On the other hand, the Helex occluder embolized more frequently **SC** (Taaffe, et al., 2008).

Another comparative study between Cardia PFO occluder, Intrasept and Amplatzer showed a residual shunting immediately following the procedure higher in patients treated with Cardia (24% vs 14% [Intrasept] and 16% [Amplatzer]; P=0,004), while the Amplatzer patients developed a new onset atrial fibrillation for the 10,1%, vs 4,9% [Cardia] and 5,3% [Intrasept]. These findings underscore the importance to effectively diagnose and treat atrial fibrillation in the postprocedural period, as this may prevent a large portion of recurrent thromboembolic events **SC** (Spies, et al., 2008).

⁴⁷ DESCRIZIONE: Relative impact of harms comparative to alternative treatment(s) for individual patients, populations, service delivery & cost effectiveness.FONTI INFORMATIVE: Other HTA reports or systematic reviews of main comparators. Manufacturer or regulators information.

Study	# patients	Atrial fibrillation	Peri-procedural stroke	Major vascular complications	Major bleeding	Death	Cardiac tamponade	Pulmonary embolism	Arrhythmia	Other embolism	Device embolization + Thrombosis on device	Device fracture/ Dislocation	Cardiac perforation
Alameddine (2004)	272	NR	NR	NR	NR	NR	NR	NR	2,2	NR	0,7	0,7	NR
Anzola (2004)	140	8,6	NR	2,9	NR	NR	NR	NR	2,1	2,1	NR	NR	NR
Braun (2004)	307	NR	NR	NR	NR	NR	NR	NR	0,7	0,7	NR	NR	NR
Fischer (2008)	154	1,3	NR	1,3	2	0,7	NR	NR	9,8	NR	2	NR	NR
Harrer (2006)	34	NR	NR	8,9	NR	3,2	NR	NR	NR	NR	NR	NR	NR
Luermans (2008)	430	NR	NR	NR	NR	0,5	0,2	NR	NR	NR	0,5	1,3	NR
Martin (2002)	110	1,8	0,9	NR	NR	2,7	0,9	1,8	NR	NR	NR	3,6	NR
Onorato (2003)	256	NR	NR	5	0,4	NR	0,4	0,8	NR	4	NR	NR	NR
Paciaroni (2011)	121	0,8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Schuchlenz (2005)	167	NR	NR	2,3	NR	0,6	1,2	NR	NR	NR	2,3	NR	NR
Sievert (2001)	281	6,2	NR	NR	NR	0,4	NR	NR	NR	NR	3,2	8,9	NR
Spies (2008) (1)	247	NR	NR	NR	NR	0,4	1	NR	1	NR	NR	NR	NR
Spies (2008) (2)	795	6	NR	NR	NR	1,1	NR	NR	NR	NR	1,4	1,8	NR
Thanopoulos (2006)	48	NR	NR	NR	NR	NR	2,1	NR	10,4	NR	NR	NR	2,1
Wahl (2008)	825	NR	NR	NR	NR	NR	NR	NR	NR	0,5	0,7	NR	NR
Wahl (2010)	150	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wahl (2012)	103	NR	NR	NR	1	6	NR	NR	NR	NR	1,3	NR	NR
Weimar (2009)	117	NR	NR	NR	NR	3,4	NR	NR	NR	NR	NR	NR	NR
Windecker (2004)	150	NR	NR	2	NR	NR	NR	NR	NR	3	4	NR	NR
Wohrle (2012)	267	1,9	NR	NR	NR	0,4	NR	NR	NR	NR	0,4	NR	NR
Furlan (2012) - CLOSURE I	402	5,7	NR	3,23	2,49	0,49	NR	NR	NR	NR	NR	NR	NR

Table 4 - Adverse events reported in clinical studies of percutaneous PFO closure (%)

Dimensions D3, D4: Efficacy and Effectiveness

Criterion C8 – Improvement of Efficacy and Effectiveness

Fonti: revisione della letteratura (pubblicazioni, registri, dati non pubblicati)

Da fare:

- Utilizzare la tabella a pagina 17 per organizzare i dati clinici prima di procedere al riassunto
- Riportare riassunti di studi pilota; se ce ne sono molti, selezionare i più rilevanti (dimensioni della popolazione, studi head-to-head con comparatori chiave)
 - Includere brevi descrizioni degli studi (tipo di studio, intervento, durata del trattamento, numero di pazienti, criteri di inclusione/esclusione, tipo di analisi, disposizioni dei pazienti)
 - Riportare sinteticamente i più rilevanti dati di efficacia in un formato facilmente comprensibile (utilizzare percentuali invece di frazioni, nelle tabelle mettere le percentuali con numeri, utilizzare cifre tonde); indicare la significatività statistica.
- Dove possibile, riportare gli outcome chiave per la metanalisi, l'efficacia e i dati osservazionali.
- Se sono disponibili solo studi che hanno come controllo il placebo, fornire un riassunto dei competitori chiave
- Dove possibile, indicare le differenze nella popolazione eleggibile attraverso interventi e comparatori

Da non fare: non includere risultati clinici da modelli di studio

SOTTOCRITERIO: Mortality

D0001 QUESITO: What is the effect of the intervention on overall mortality?⁴⁸

Mortality after the intervention has shown to have a low rate, since death is usually related to other diseases which can affect the patient. Furthermore, percutaneous PFO closure has been shown to be safer than surgical closure, thus avoiding the major complications due to the more invasive procedure.

In CLOSURE I, the only randomized controlled trial available at the moment, the primary composite end-point of a reduction in stroke, TIA, and mortality at 2 years was reached in 5,9% of patients in the device arm and 7,7% of patients in the medical treatment arm ($p < 0,30$) **RCT** (Furlan, et al., 2012).

It's important to note that only a few studies are available on recurrence of thromboembolic events in older patients, i.e. with age > 55 years. Due to the greater number of competing causes of stroke, the question of the relationship between PFO and cryptogenic stroke is more difficult to answer for older patients. However, some studies consistently corroborate the association of PFO and cryptogenic stroke not only in younger patients, but also in older ones, thus showing a greater risk for the latter ones, even more with concomitant ASA, as a predictor for the degree of the right-to-left shunt through a PFO (2 years adverse event rates in PFO patients aged less than 55 years vs PFO patients aged 55 to 64 years for death/stroke: 2% vs 10%; death/stroke/TIA: 12,2% vs 10%; stroke/TIA: 12,2% vs 5%; stroke: 2% vs 5%) **R** (Handke, et al., 2009) **E** (Handke, et al., 2007) **E** (Homma, et al., 2004).

D0002 QUESITO: What is the effect of the intervention on the mortality caused by the target disease?⁴⁹

See QUESITO D0001

D0003 QUESITO: What is the effect of the intervention on the mortality due to other causes than the target disease?⁵⁰

SOTTOCRITERIO: Morbidity

D0005 QUESITO: How does the intervention modify the severity and frequency of symptoms and findings?⁵¹

⁴⁸ DESCRIZIONE: Use of technology may have an impact on patients' life expectancy. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data.

⁴⁹ DESCRIZIONE: Use of technology may have an impact on mortality caused by the target disease. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data.

⁵⁰ DESCRIZIONE: Use of technology may have an impact on the mortality due to other causes than the target diseases. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews. Health care register data.

CLOSURE I (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale) is the only prospective, multicenter, randomized, open-label, two-group superiority trial available at the moment which evaluates the potential benefit of a percutaneous device as compared with medical therapy for closure of a patent foramen ovale with cryptogenic stroke or TIA.

The primary end points of the device closure of PFO were stroke or transient ischemic attack (TIA). In this randomized controlled trial, the Kaplan–Meier estimate of the **cumulative incidence of the primary end point in the intention-to-treat population after 2 years** of follow-up was **5,5%** in the closure group and **6,8%** in the medical-therapy group (adjusted hazard ratio, 0,78; 95% confidence interval [CI], 0,45 to 1,35; P = 0,37). The Kaplan–Meier estimates of **2-year rates of stroke** were **2,9%** in the closure group and **3,1%** in the medical-therapy group (adjusted hazard ratio, 0,90; 95% CI, 0,41 to 1,98), with respective rates of **3,1% and 4,1% for TIA** (adjusted hazard ratio, 0,75; 95% CI, 0,36 to 1.55). No deaths had occurred at 30 days in either group, and there were no deaths from neurologic causes during the 2-year follow-up period, furthermore it was not found significant effect of the presence or absence of atrial septal aneurysm or the degree of shunting on the primary end point.

Thus, these results did not demonstrate a benefit of PFO closure with the STARFlex device compared with medical therapy, and individually, stroke or TIA were not statistically different between the 2 treatment arms, as shown in the figure below **RCT** (Furlan, et al., 2012).

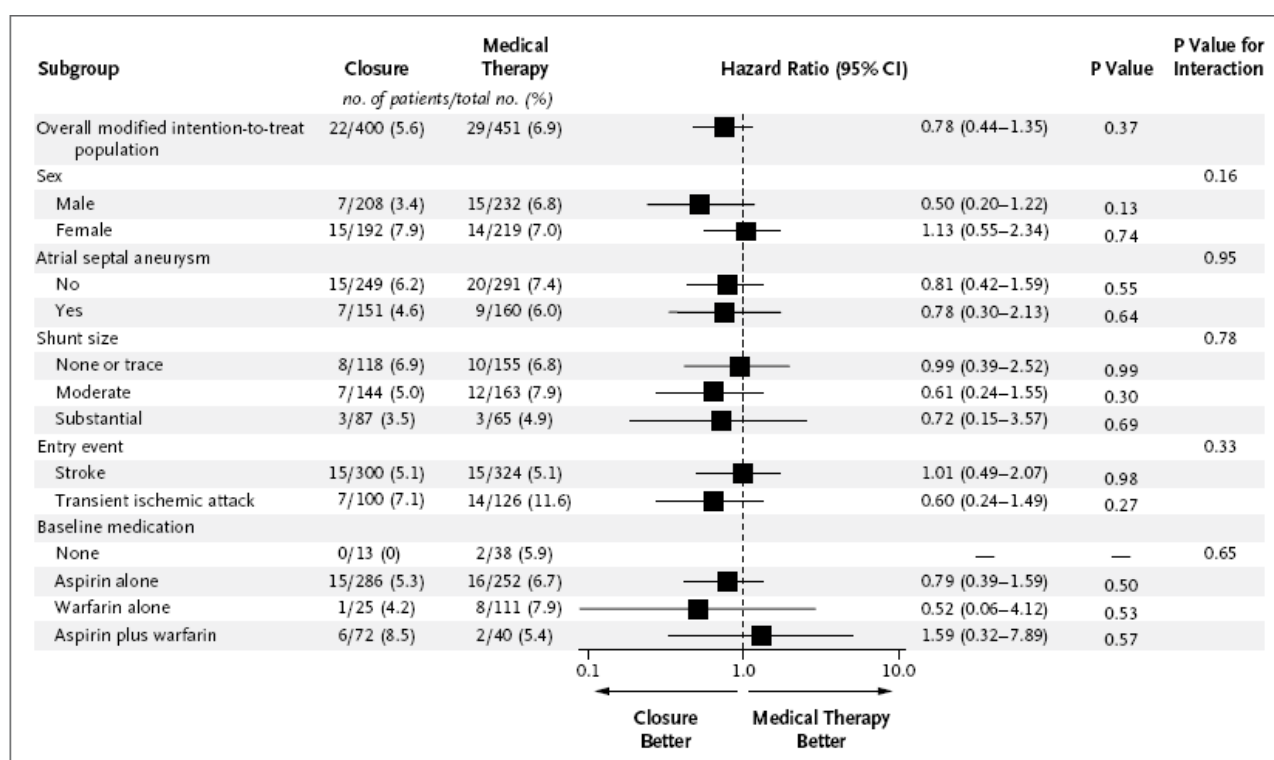


Figure 3 - Results of primary end point analysis at 2 years, according to subgroup (percentages in parentheses are Kaplan–Meier estimates of the event rates)

On the contrary, observational and randomized evidence point to different conclusions regarding treatment efficacy of closure. Case series and nonrandomized comparisons have long suggested that closure is a highly efficacious procedure and have led to the rapid adoption of this intervention by some clinical practitioners.

The summary Incidence Rate (IR) of recurrent strokes in closure studies is 0,36 events (95% CI, 0,24–0,56) per 100 person-years, whereas the summary IR from medical studies is much higher at 2,53 events (95% CI, 1,91–3,35) per 100 person-years. Both meta-analytic estimates are characterized by a significant statistical heterogeneity (P<0,001), as shown in the figure below **R** (Kitsios, et al., 2012).

⁵¹ DESCRIZIONE: Use of technology may have an impact on patients' symptoms. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

Outcome	Observational Studies				Randomized Clinical Trial (CLOSURE I)		
	Closure Arm IR (95% CI), per 100 Person-Years	Medical Arm IR (95% CI), per 100 Person-Years	IRR (95% CI) Closure vs Medical (Comparative Studies Only)	IRR (95% CI) Closure vs Medical (All Studies)	Closure Arm IR (95% CI), per 100 Person-Years	Medical Arm IR (95% CI), per 100 Person-Years	HR (95% CI) Closure vs Medical
Total events	0.80 (0.55–1.18)	4.73 (3.41–6.56)	0.22 (0.07–0.64)	0.17 (0.10–0.28)	2.79 (1.81–4.13)	3.25 (2.19–4.63)	0.76 (0.45–1.29)
Stroke events	0.36 (0.24–0.56)	2.53 (1.91–3.35)	0.19 (0.07–0.54)	0.14 (0.08–0.24)	1.34 (0.69–2.34)	1.41 (0.74–2.41)	0.89 (0.41–1.95)
TIA events	0.46 (0.29–0.74)	1.93 (1.16–3.20)	0.15 (0.02–1.35)	0.24 (0.12–0.47)	1.45 (0.77–2.49)	1.83 (1.10–2.94)	0.73 (0.35–1.50)

For observational studies, results are presented separately for meta-analyses of incidence rates of events (stroke and transient ischemic attack) from single-arm studies and for meta-analyses of incidence rate ratios from comparative studies (with or without considering the evidence from single arm studies).

CI indicates confidence interval; HR, hazard ratio; IR, incidence rate; IRR, incidence rate ratio; TIA, transient ischemic attack.

Figure 4 - Summary Estimates Derived From Meta-Analyses of Observational Studies and Estimates Extracted From the CLOSURE I Trial

A meta-analysis of 48 observational studies comparing transcatheter closure and medical therapy reported adjusted incidence rates of recurrent neurological events (RNE) of 0,8 (95% confidence interval [CI]: 0,5 to 1,1) events and 5,0 (95% CI: 3,6 to 6,9) events/100 person-years (PY) in the transcatheter closure and medical management arms, respectively. Despite the limited number of comparative studies, the meta-regression analysis suggested that the transcatheter closure might be superior to the medical therapy in prevention of RNE after cryptogenic stroke **R** (Agarwal, et al., 2012).

In contrast, the randomized trial failed to identify any statistically significant difference between closure and medical therapy. In their way, **C** (Windecker, et al., 2004) had already reported in their comparative study that there was no significant difference in the risk of recurrent stroke or TIA between percutaneous PFO closure and medical treatment (see Figure 4). The discrepancy between the major findings of these types of studies, observational and randomized, may be a reflection of inherent limitations of observational evidence. It is well-appreciated that confounding by indication can create noncomparable populations in the medical and closure treatment arms, in terms of the underlying risk of the outcomes of interest for the patients. Thus, nonrandomized groups of patients may vary in the distribution of factors that determine both the likelihood that the index event was PFO-related and also the risk of a recurrent event. However, RCT may fail to reject the null hypothesis for numerous reasons, with limited statistical power as a primary concern. For instance, idiosyncratic effects of the STARFlex device, such as in situ thrombosis or other mechanical complications, may have also increased the outcome rates in the CLOSURE I intervention arm **R** (Kitsios, et al., 2012).

The theory that closure is not always the right solution for preventing stroke recurrence is highlighted by two recent meta-analyses. Using Bayes' theorem, the summary probability that a PFO is incidental in patients with cryptogenic stroke was **33%** (28% to 39%) in age-inclusive studies. The corresponding probability was 20% (16% to 25%) for younger patients and 48% (34% to 66%) for older patients. A PFO was less likely an incidental finding when a concomitant ASA was detected with the probability of it being incidental estimated at 11% (4% to 31%) from age-inclusive studies, 9% (4% to 18%) in younger patients, and 26% (12% to 56%) in older patients, enforcing the results shown in many studies that atrial septal aneurysm (ASA) is associated to patent foramen ovale, thus increasing the recurrence event rate **E** (Mattioli, et al., 2001) **M** (Almekhlafi, et al., 2009) **M** (Alsheikh-Ali, et al., 2009).

Moreover, risk stratification strategies for PFO closure, however, need to include stratification not only for stroke recurrence risk but also, more importantly, for the probability that the index event is itself PFO attributable **R** (Kent, et al., 2010).

The table in the following pages (Table 5) summarizes the primary end points of the most important comparative and observational studies, in juxtaposition with CLOSURE I, including the annual recurrence rate, where reported.

Migraine

Over the past decade, there have been 17 reported observational studies evaluating the effect of percutaneous PFO closure on migraine headaches. A pooled analysis of these 866 people reveals that 83% had either complete cessation of migraines or a clinically significant reduction (defined as > 50% reduction in headache days/month). The number of patients suffering from migraine with aura who responded was approximately 2-fold greater than those who had migraine without aura **R** (Tobis, et al., 2012).

The only completed randomized trial of PFO closure for migraine headaches is the MIST (Migraine Intervention with STARFlex Technology) Trial. The MIST trial enrolled 147 patients, presenting migraine with aura and no history of previous paradoxical embolization, who were randomized 1:1 to device closure with the STARFlex septal implant or a sham procedure consisting of a skin incision in the groin under general anesthesia. Patients averaged 5 migraine attacks/month with 30 headache days over a 3-month period. After 6 months, the primary endpoint of complete cessation of migraine headaches after device closure, which was derived from diary data, was not reached, because only 3 patients in each group reported no further migraine headaches. The secondary endpoints, which included the incidence, frequency, and severity of migraine attacks were also not met in this trial.

Exploratory analysis was undertaken when it was evident that 2 statistical outliers accounted for more than one third of the overall migraine headaches experienced. When these 2 patients were removed, the implant arm demonstrated a significant reduction in total migraine headache days, consistent with but not proof of a causal relationship between PFO and migraine with aura. Some patients may benefit from closure, but a potential for short-term deterioration exists in a minority of patients **RCT** (Dowson, et al., 2008).

Results of the trial are reported in the figure below:

	Implant (n=74)		Sham procedure (n=73)		Statistical Analyses*	
	Baseline	Analysis Phase	Baseline	Analysis Phase	Difference Between Implant and Sham Arms (95% CI)	P
Patients with no migraine attacks, n	0	3	1	3	-0.06% (-6.45-6.34)	1.0
Frequency of migraine attacks/mo, mean±SD	4.82±2.44	3.23±1.80	4.51±2.17	3.53±2.13	0.45 (-0.16-1.05)	0.14
n	66	66	73	73	...	...
Total MIDAS score, median (range)	36 (3-108)	17 (0-270)	34 (2-189)	18 (0-240)	1 (-11-10)	0.88
n	66	67	69	72	...	...
Headache d/3 mo (MIDAS), median (range)	27 (0-70)	18 (0-90)	30 (5-80)	21 (0-80)	1 (-5-6)	0.79
n	66	67	69	72	...	...
HIT-6 total score, mean±SD	67.2±4.7	59.5±9.3	66.2±5.1	58.5±8.6	0 (-3-2)	0.77
n	67	67	69	73	...	...

Missing data were replaced by last observation carried forward. CI indicates confidence interval.

Figure 5 - Efficacy analysis in the MIST trial

The MIST trial has been extensively critiqued for methodological design and credibility. The patient population enrolled included those with chronic headaches, a subgroup that might not respond to conventional therapies, because the headache etiology is obscured with over-medication and drug withdrawal headache. The follow-up period of 3 to 6 months might be too brief, because percutaneous PFO closure devices might require more time to endothelialize and eliminate shunting through a PFO. Only contrast transthoracic echocardiograms (TTEs) were obtained at follow-up, which is less sensitive than TEE or transcranial Doppler detection of right-to-left shunting.

There is also significant controversy about the true incidence of residual shunts, which damages the credibility of the study. Although the MIST I trial reported a 5% residual shunt in the device arm at 6 months, one of the principle investigators alleges that 35% of device-treated patients had a large residual shunt. Given that there was no independent echocardiography core laboratory, these allegations are matters of concern and require cautious interpretation of the MIST trial **R** (Tobis, et al., 2012).

In many retrospective monocentric studies, enrolling patients with presumed paradoxical embolism, PFO closure determined a resolution of migraine in 46% of cases and an improvement of symptomatology in 83% of patients **M** (Butera, et al., 2010). Nonetheless, due to short follow up (range of 3-12 months) and antiaggregant therapy for 6 months after closure (which have been shown to provide considerable benefits in migraine treatment by itself), the effectiveness of PFO closure on migraine is still difficult to define. Recently, **SC** (Rigatelli, et al., 2010) enrolled a group of 86 patients reporting migraine refractory to medical therapy and PFO with high risk features, both anatomical and functional (among which ASA, Eustachian Valve, evidence of shunt at rest, coagulation anomalies); 40 patients were subjected to PFO closure, while 46 refused interventional treatment and were used as control group with medical therapy. After a mean follow up of 2 years, only patients which underwent PFO closure reported an improvement in migraine symptomatology at MIDAS

questionnaire (Migraine Disability Assessment Score); in particular, patients with aura (32/40, 80%) informed of a total resolution of symptoms.

According to the results of another observational trial by **SC** (Wahl, et al., 2010), one can assume that, if a patient with migraine, and especially migraine with aura, undergoes PFO closure for another reason than his migraine, it is more likely that he will experience some improvement than that there will be no change or even worsening of his headaches. Furthermore, recurrence of migraine, once it has responded to PFO closure, will be unlikely.

In 17 patients with migraine headaches refractory to medical treatment undergoing percutaneous PFO closure solely for attempted treatment of their headaches, similar results have been recently reported by the same authors, with complete cessation of headaches in 24% of patients, persisting but improved headaches in 47% and unchanged headaches in 29%. Overall, the prevalence of any migraine headaches decreased from 100% to 76%, and the prevalence of migraine with aura from 82% to 24% ($p=0,002$). On the other hand, as it was already stated, the MIST trial, including 147 patients with drug-resistant migraine with aura, failed to reach both its primary and secondary end points, with only 4% of patients “cured” in each group at 6 months follow up.

Hence, to this day patients with migraine with aura without previous paradoxical embolism represent a population for which PFO closure doesn't guarantee any benefit. The intervention, currently off-label, could be taken into consideration in the future for high risk patients with indicative clinical features or refractoriness to medical therapy **R** (Balbi, et al., 2010).

D0006 QUESITO: How does the intervention modify the progression of disease?⁵²

PFO closure is aimed at preventing recurrence of cerebrovascular accidents (CVAs) and thromboembolic events, as many clinical trials reported it to be safe and effective, with high success rate, low incidence of periprocedural complications and excellent results during long-term follow up **R** (Khairy, et al., 2003).

In questo quesito sono ricompresi:

- 1) gli outcomes di morbidità esclusa la mortalità (ad esempio in area cardiovascolare gli eventi importanti quali infarto miocardico acuto o ictus cerebri)
- 2) gli outcomes intermedi tipicamente misurabili con end point surrogati (ad esempio in area cardiovascolare lo spessore medio intimale delle carotidi)

D0007 QUESITO: How does the intervention modify the recurrence of symptoms and findings?⁵³

See QUESITO D0005

SOTTOCRITERIO: Questions about effectiveness and accuracy

F0017 QUESITO: What are the proper end-points for assessment and how should they be investigated?⁵⁴

Primary endpoints for the intervention are neurologist-confirmed recurrence of cerebrovascular accidents (CVAs), TIAs and death. In some cases, functional disability following CVA was also assessed with the Lausanne scale, which includes the following categories: no sequelae, minor sequelae such that all previous activities can be performed, moderate sequelae that limit previous activities, and severe sequelae, such that no previous activities can be performed **SM** (Bogousslavsky, et al., 1996) **SM** (Cujec, et al., 1999).

Secondary end points to be investigated are usually new arrhythmia, myocardial infarction, rehospitalization related to PFO or its treatment, device problems such as dislodgment, structural failure, infection, thrombosis,

⁵² DESCRIZIONE: Use of technology may have an impact on course of the illness. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

⁵³ DESCRIZIONE: Use of technology may have an impact on course of the illness.

⁵⁴ DESCRIZIONE: For diagnostic tests, clinical effectiveness should ideally be directly investigated, but this is not always fully possible so other endpoints may have to be used. In addition, diagnostic tests may have several aims (e.g. those related to knowledge without expected health effects). The acceptable and feasible endpoints (possibly several) for assessing diagnostic technologies must be carefully considered early in the analysis. The context-specificity of diagnostic technologies must be especially considered; for example, results of diagnostic technologies are rarely in practice interpreted without knowing the clinical and organisational situation of the patient, some technologies require extensive interpretative skills, and the practical consequences of diagnostic tests will depend on the population tested. The importance of context relates to what kinds of studies are deemed acceptable. FONTI INFORMATIVE: Other domains of analysis: accuracy, safety, effectiveness. Expert opinion.

etc., and bleeding complications related to antithrombotic therapy classified as severe, when requiring any blood transfusion, and minor, when not requiring blood transfusions **R** (Khattab, et al., 2011).

Assessments of clinical end points and adverse events are usually planned at 1 month, 6 months, 12 months, and 1 year after closure by using transesophageal echocardiogram (TEE), fluoroscopy and chest x-ray in order to determine the presence and/or extent of right-to-left shunt and exclude thrombosis of the device **RCT** (Furlan, et al., 2012). Transcranial Doppler constitutes an alternative **R** (Meier, et al., 2012). In particular, when assessing completeness of closure with TEE, Valsalva is therefore implemented, followed by a bubble test at 6 months of follow-up. Provided a satisfactory result of the 6-month contrast TEE, antithrombotic therapy and the recommendation for prophylaxis against endocarditis is discontinued, unless required by another indication **R** (Khattab, et al., 2011).

F0018 QUESITO: Are the accuracy measures decided and balanced on a transparent and acceptable way?⁵⁵

Evaluation criteria are measurable.

SOTTOCRITERIO: Training and information needed for utilizing the technology

B0020 QUESITO: How does training and quality assurance affect the management or effectiveness?

The variation in devices and the use of some devices that are obsolete, even though they are standard of care when PFO closure is introduced in a certain hospital, represent limitations for proper endpoints and results for clinical studies; improved devices, techniques and accompanying drugs have yielded annual recurrence rates <1%.

As for medical treatment, novel oral anticoagulants such as dabigatran, are easier to administer and may be associated with improved clinical outcome. However, a bleeding risk persists **C** (Wahl, et al., 2012).

⁵⁵ DESCRIZIONE: Are the accuracy measures chosen so that they accord with the purpose of the HTA? How and by whom are cut-off values decided? How and by whom has balancing sensitivity and specificity been done? This should be done considering the moral value of different results – for example, high specificity is required if false positives have serious consequences. FONTI INFORMATIVE: Other domains of analysis: accuracy, safety, effectiveness. Expert opinion.

Study	Design	# patients	Mean age	% males	% ASA	Treatment	% antiplatelet	% anticoagulation	Device used	Follow up (months)	# recurrent total events	# recurrent strokes	# recurrent TIAs	Annual recurrence rate stroke+TIA	Annual recurrence rate strokes	Annual recurrence rate TIAs	P Value
Comparative Studies																	
Harrer (2006)	Prospective	34	49,5	44,1	32,4	Closure			Rashkind Occluder, Sideris Device, Amplatzer-Septal Occluder	52	2	2	0	2,9	NR	NR	> 0,05
	Retrospective	83	51,1	77,3	NR	Medical	52	48			8	6	2	2,1	NR	NR	
Paciaroni (2011)	Prospective	121	43,4	59	62	Closure			Amplatzer PFO Occluder, PFO STAR, CardioSEAL/STARFlex	24	7	1	6	2,9	0,4	NR	0,1; 0,053
	Prospective	117	40,9	59	41	Medical	79,5	20,5			10	8	2	4,2	3,4	NR	
Schuchlenz (2005)	Prospective	167	44	53,6	25,1	Closure			Rashkind Occluder, CardioSEAL, STARFlex, Amplatzer Septal-Occluder, Amplatzer PFO Occluder	31,2	2	1	1	0,6	NR	NR	NR
	Prospective	113	48	54,9	24	Medical	58,4	41,6			31	8	23	10,5	NR	NR	
Thanopoulos (2006)	Prospective	48	43	56	27	Closure			Amplatzer PFO Occluder	24	0	0	0	0	0	0	0,004; 0,001
	Prospective	44	40	48	23	Medical	100	NR			13	7	6	14,7	8	6,8	
Wahl (2012)	Prospective	150	50	53,8	24,7	Closure			Amplatzer PFO, PFO STAR, Sideris Buttoned, Angel Wing, Amplatzer ASD, CardioSEAL	108	11	6	5	1,3	0,8	0,5	0,001; 0,6; 0,001
	Prospective	158	50,7	58,2	22,2	Medical	55	45			22	8	14	3,7	1	2,7	
Weimar (2009)	Prospective	117	46	62,3	28,7	Closure			NR	28,4	2	2	0	0,7	NR	NR	NR
	Prospective	234	57	65,8	20	Medical	65,8	26,9			20	20	0	3,7	NR	NR	NR

Windecker (2004)	Prospective	150	50	53	25	Closure			Amplatzer PFO Occluder, PFO STAR, Sideris Device, Angel Wing Device, Amplatzer-Septal Occluder, CardioSEAL	48	9	2	7	1,5	0,3	1,2	0,08; 0,19; 0,23
	Prospective	158	51	58	22	Medical	50	50			21	7	14	3,3	1,1	2,2	
Single Arm Closure Studies																	
Alameddine (2004)	Prospective	272	51	52,9	32,7	Closure			CardioSEAL, STARFlex	6	5	3	2	NR	NR	NR	NR
Anzola (2004)	Prospective	140	46	45	47	Closure			Amplatzer PFO Occluder, Helex Septal Occluder, PFO STAR	12	1	0	1	NR	NR	0,7	NR
Braun (2004)	Prospective	307	43	55	23	Closure			PFO-Star, Amplatzer PFO Occluder, CardioSEAL/STARFlex	24	4	0	4	0,8	0	0,7	NR
Fischer (2008)	Prospective	154	43,9	61	37	Closure			STARFlex	26	9	2	7	2,6	0,6	2,1	NR
Luermans (2008)	Prospective	430	50,7	53,7	45,4	Closure			Intrasept	9,6	9	2	7	NR	NR	NR	NR
Martin (2002)	Prospective	110	47	53	14,5	Closure			Sideris Device, CardioSEAL	27,6	2	1	1	NR	NR	NR	NR
Onorato (2003)	Prospective	256	48	41	34,6	Closure			Amplatzer PFO Occluder, Helex Septal Occluder, PFO STAR	19	0	0	0	NR	NR	NR	NR
Sievert (2001)	Retrospective	281	46,8	NR	22,8	Closure			Sideris Device, ASDOS device, Angel Wings Device, CardioSEAL, CardioSEAL/STARFlex, Amplatzer, Helex	12	9	2	7	3,3	0,8	2,6	NR
Spies (2008) (1)	Prospective	247	53	53,4	51,4	Closure			Intrasept	14	7	3	4	2	NR	NR	NR
Spies (2008) (2)	Prospective	795	51	53	46	Closure			Cardia, Intrasept, Amplatzer	26	24	9	15	1,4	0,5	0,9	NR

Wahl (2008)	Prospective	825	51	58	29	Closure			Sideris Device, Angel Wing Device, Amplatzer Septal Occluder, CardioSEAL/STARFlex, PFO-STAR/Cardia-STAR Septal Occluder, Amplatzer PFO Occluder, Helex, Premere	6	1	0	1	0	0	0,2	NR
Wahl (2010)	Retrospective	150	51	54	40	Closure			Amplatzer PFO Occluder	108	2	1	1	0,1	0,1	0,1	NR
Wohrle (2012)	Prospective	267	48	51,7	39	Closure			Premere	11	0	0	0	0	0	0	NR
Single Arm Medical Studies																	
Bogousslavsky (1996)	Retrospective	140	44	59,3	NR	Medical	66	26		36	16	8	8	3,8	1,9	1,9	NR
Cujec (1999)	Retrospective	52	38	60	11,5	Medical	69	73		43	19	7	12	6,2	NR	NR	NR
Homma (2002) - PICSS	Prospective	630	59	55,2	11,5	Medical	50,5	49,5		24	105	71	34	8,3	5,6	2,7	NR
Mas (1995)	Retrospective	107	40,4	50,5	35,5	Medical	44,7	25		22,6	5	2	3	3,4	1,2	NR	NR
Mas (2001)	Prospective	267	40,3	52,7	19,1	Medical	98	NR		27,8	21	12	9	3,4	1,9	1,5	0,07
Serena (2008)	Prospective	286	53,6	62	38,3	Medical	79	21		24,3	ND	28	ND	ND	4,8	ND	NR
Randomized Controlled Trials																	
Furlan (2012) - CLOSURE I	Prospective	447	46,3	52,1	37,6	Closure			STARFlex device	24	25	12	13	2,6	1,3	1,5	0,37; 0,79; 0,44
	Prospective	462	45,7	51,5	35,7	Medical	64,7	33,5			30	13	17	3,1	1,4	1,8	

Table 5 - Baseline characteristics, types of treatment in closure and medical studies, and their respective primary outcomes

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Criterion C9 – Improvement of patient related outcomes

Fonti: revisione della letteratura (pubblicazioni, lavori con dati non pubblicati)

Da fare:

- Riportare i dati di outcome riportati dal paziente sulla tecnologia e i comparatori in formato tabellare (popolazione, strumenti usati, outcome riportati, durata del trattamento)
- Specificare se gli strumenti utilizzati sono validati per la popolazione
- Indicare i dati di convenienza/aderenza del paziente per l'a tecnologia e il comparatore

Da non fare: non includere la convenienza o l'aderenza alle linee guida del fornitore del servizio sanitario (segnalare solo la prospettiva del paziente)

SOTTOCRITERIO: Patient satisfaction

D0017 QUESITO: Was the use of technology worth it?⁵⁶

D0018 QUESITO: Would the patient be willing to use the technology again?⁵⁷

PFO closure can be preferred since the avoidance of a life-long anticoagulant treatment is an advantage that convinces many physicians as well as patients **SC** (Sievert, et al., 2001).

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Criterion C10 – Guidelines & good practice recommendations

Fonti: revisione della letteratura (associazioni, siti web [ad es. agenzie di HTA, organi decisionali])

Da fare:

- Riportare le più recenti linee guida cliniche (specifiche per paese o internazionali) che riportano il tipo di intervento e la raccomandazione (fortemente raccomandato, raccomandato in seconda linea, etc)
- Indicare quale organizzazione ha sviluppato le linee guida, la metodologia, l'impostazione, i partecipanti, i finanziamenti
- Se non ci fossero linee guida, identificare revisioni della letteratura o rapporti di HTA in modo da avere una base di partenza
- Includere informazioni sulle decisioni prese da altre giurisdizioni

SOTTOCRITERIO: Current Management of the Condition

A0016 QUESITO: According to algorithms/guidelines (if any), how should the condition be managed?⁵⁸

The management of cerebrovascular events with PFO has revolved around three treatment options: medical treatment with anticoagulation or antiplatelet therapy, surgical closure, and percutaneous closure.

For patients who have had a cryptogenic stroke and have a PFO, the evidence indicates that the risk of subsequent stroke or death is no different from other cryptogenic stroke patients without PFO when treated medically with antiplatelet agents or anticoagulants. Therefore, in persons with a cryptogenic stroke receiving such therapy, neurologists should communicate to patients and their families that presence of PFO does not confer an increased risk for subsequent stroke compared to other cryptogenic stroke patients without atrial abnormalities. However, it is possible that the combination of PFO and ASA confers an increased risk of subsequent stroke in medically treated patients who are less than 55 years of age **G** (Messé, et al., 2004).

ASA is frequently associated with PFO. In patients with cerebral ischemia and ASA, ASA (with or without PFO) is often the only potential cardioembolic source identified on TEE. Concomitant presence of an ASA, small additional atrial septal defects, a large Eustachian Valve, or Chiari strands have all been postulated (but not conclusively proven) to be significant in the presence of a PFO. Chiari strands, congenital remnants of the right valve of the sinus venosus, can be associated with both PFO and ASA, and are believed by some to facilitate paradoxical embolism **R** (Kutty, et al., 2012).

⁵⁶ DESCRIZIONE: Patients overall assessment of the worthiness of the intervention. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

⁵⁷ DESCRIZIONE: Patients overall assessment of the worthiness of the intervention. FONTI INFORMATIVE: Systematic reviews of RCTs (Randomised controlled trials) or CTs (controlled trials), if not available RCTs or CTs itself. If these not available, non-controlled studies and respective systematic reviews.

⁵⁸ DESCRIZIONE: Assessment of this allows to draw conclusions on how far the current management is optimal. FONTI INFORMATIVE: Clinical Guidelines, recommendations. If such information is lacking: Expert surveys / expert interviews, textbooks.

The combination of PFO and ASA emerged as a predictor of increased risk for recurrent stroke in some reports **SM** (Mas, et al., 2001) **E** (Handke, et al., 2007), but in other studies, neither PFO alone nor in combination with ASA was associated with an increased risk for stroke **E** (Di Tullio, et al., 2007). The association of ASA with stroke recurrence remains debatable. **SM** (Homma, et al., 2002) demonstrated that neither the degree of shunt nor concomitant ASA is associated with an increased risk of stroke recurrence or death. Published literature is also inconsistent regarding foramen size as a cryptogenic stroke risk factor **R** (Kutty, et al., 2012).

However, some studies suggest reserving closure for patients with markers of increased risk of recurrent stroke, which may include a history consistent with paradoxical embolism, recurrent events despite medical therapy, the combination of PFO and ASA, large PFO size, or an underlying hypercoagulable state **M** (Almekhlafi, et al., 2009).

Recommendations in US

Both the American Heart Association/American Stroke Association (AHA/ASA) and American College of Chest Physicians (ACCP) guidelines recommend antiplatelet therapy for patients with ischemic stroke or transient ischemic attack and PFO (AHA/ASA Class IIa, level of evidence: B; ACCP grade 1A), unless other indications exist for vitamin K antagonist therapy (e.g., atrial fibrillation, hypercoagulable state; AHA/ASA Class IIa, Level of Evidence: C; ACCP grade 1C). The AHA/ASA guidelines for secondary stroke prevention state that “insufficient data exist to make a recommendation about PFO closure in patients with a first stroke and a PFO. PFO closure may be considered for patients with recurrent cryptogenic stroke despite medical therapy (Class IIb, Level of Evidence: C)” **R** (O’Gara, et al., 2009) **R** (Mattle, et al., 2010).

The American Academy of Neurology (AAN) asserts these recommendations: PFO is not associated with an increased risk of subsequent stroke or death among medically treated patients with cryptogenic stroke. The co-incidence of PFO and ASA possibly increases the risk of subsequent stroke (but not death) in medically treated patients aged <55 years. In patients with a cryptogenic stroke and an atrial septal abnormality (PFO, ASD, or ASA), the evidence is insufficient to determine whether warfarin or acetylsalicylic acid is superior in preventing recurrent stroke or death, but minor bleeding is more frequent with warfarin. There is insufficient evidence to evaluate the efficacy of surgical or endovascular closure **G** (Messé, et al., 2004).

Recommendations in EUROPE

EUROPEAN STROKE ORGANISATION - ESO

Antiplatelet therapy is recommended after TIA or stroke. In the presence of proven deep vein thrombosis (DVT) or atrial septal aneurysm, anticoagulation is recommended [Class IV, good clinical practice (GCP)]. Consider endovascular closure of PFO in patients with cryptogenic stroke and high-risk PFO (Class IV, GCP) guidelines.

It’s important to note that the definition of “high-risk” patients is open **R** (Mattle, et al., 2010).

Italy

SPREAD (Stroke Prevention and Educational Awareness Diffusion) guidelines for Italy determine these practices **G** (SPREAD, 2012):

- For patients with an ischemic cryptogenic stroke or TIA and a PFO without deep vein thrombosis or thrombophilic disorders Aspirin 325 mg once daily is indicated (Level of Evidence A).
- For patients with an ischemic cryptogenic stroke or TIA and a PFO with other indications for oral anticoagulant therapy such as deep vein thrombosis or thrombophilic disorders Warfarin is indicated (Level of Evidence A).
- For patients with an ischemic cryptogenic stroke or TIA and a PFO with deep vein thrombosis or thrombophilic disorders and contraindications for oral anticoagulant therapy PFO closure is indicated (Level of Evidence D).
- For patients with cryptogenic stroke recurrence in the presence of therapy with Aspirin or Warfarin, PFO closure is indicated after a multidisciplinary case examination and patient agreement. (Good practice point).

However, a Position statement by the Italian Society of Invasive Cardiology (SICI-GISE); Italian Stroke Association (ISA-AIS); Italian Association of Hospital Neurologists, Neuroradiologists, Neurosurgeons (SNO); Congenital Heart Disease Study Group of Italian Society Of Cardiology; Italian Association Of Hospital Cardiologists (ANMCO); Italian Society Of Pediatric Cardiology (SICP); Italian Society of Cardiovascular Echography (SIEC); Italian Society of Hemostasis and Thrombosis (SISCT) has been published in August 2012

with these indications (SOURCES OF FUNDING: Meeting expenses were provided by AGA medical Italy, St. Jude Medical Italy, Occlutech Italy, Biosense Webster Italy) **G** (Pristipino, et al., 2012)

THERAPY	1. Consistent with international guidelines, we recommend that patients with PFO and cryptogenic stroke/TIA be treated with antiplatelet therapy, unless all the following conditions are present: a percutaneous closure has been successfully performed, the PFO residual patency has been excluded at follow up and the antiplatelet withdrawal is considered safe by the heart-brain team (i.e. in case of the highest probability of paradoxical embolization as the cause of an index event). 2. Oral anticoagulant therapy with vitamin K antagonists should be considered instead of antiplatelet therapy in patients with specific conditions such as recurrent ischemic events, coexisting atrial septal aneurysm, prothrombotic inherited alterations, or antiphospholipid syndrome. In these cases, anticoagulant therapy may be provided if the risk of bleeding is low, proper anticoagulant monitoring can be performed, and patient compliance is satisfactory. 3. We recommend anticoagulant therapy in patients with cryptogenic stroke or TIA and PFO who also have clinical conditions that require anticoagulant therapy such as venous thromboembolism. 4. Although studies are limited, it may be prudent to consider anticoagulant therapy for patients who have had an ischemic event while under antiplatelet treatment or when percutaneous closure is either contraindicated or refused by the patient.
INTERVENTIONAL TREATMENT	1. Pending completion of a diagnostic evaluation for patency of a foramen ovale, we recommend that patients with cryptogenic stroke or TIA be treated with medical therapy (antiplatelet or anticoagulant drugs, as appropriate). 2. In patients with an initial event, who have no anatomic or clinical risk factor (such as multiple ischemic lesions on computer tomography scan/magnetic resonance imaging, recurrent clinical events, history of deep vein thrombosis/pulmonary embolism and/or thrombophilia, valsalva-associated embolic event, ischemic event on arousal (OSAS - obstructive sleep apnea syndrome), long travel/immobilization associated event, simultaneous systemic/pulmonary embolism), we recommend treatment with the appropriate medical therapy. 3. In patients with an initial event, who have one or more anatomic or clinical risk factors, we recommend percutaneous closure of the PFO be offered as an alternative to life-long medical therapy. Patients should be informed that contemporary data show that closure of the PFO is no more effective than medical therapy in preventing recurrence at two years. 4. In patients with an initial or recurrent cryptogenic ischemic event, who already are on antiplatelet drugs, we recommend that transcatheter closure of the PFO be offered. If the interventional procedure is contraindicated, or if the patient declines the procedure, the patient may undergo anticoagulant therapy instead of antiplatelet therapy. 5. Transcatheter closure of the PFO is indicated in patients with an initial or recurrent ischemic event while on anticoagulants. 6. Patients with a cryptogenic stroke or TIA who should subsequently undergo chronic anticoagulation because of other concomitant reasons (eg. recurrent pulmonary embolism, thrombophilia, or antiphospholipid antibody syndrome) should not be offered interventional treatment unless the neurological event is a recurrence occurred while already on anticoagulants. Percutaneous closure can be offered in case of the need of stopping anticoagulation. 7. Patients who had previous percutaneous closure of a PFO, but who have at 6 months after the procedure a significant (moderate or severe) residual shunt, which is unchanged as compared to before the procedure, can be considered for immediate repeat procedure according to the baseline clinical risk of the patient. Patients who reduced the degree of shunt at 6 months after the procedure (to a mild or moderate degree) should be considered for repeat percutaneous closure only after a recurrent cryptogenic stroke.

RECOMMENDATIONS FOR PREVENTION OF COMPLICATIONS	Through device selection As some devices for closure of PFO may better fit specific anatomic conditions, in the absence of controlled data it is reasonable to suggest that effort should be put to select the device on an individual basis according to anatomic characteristics. Size and type of device selection also may be influenced by other patient factors such as clotting disorders and vulnerability to atrial fibrillation.
	Through ultrasound guidance Despite some non-randomized report described the feasibility of percutaneous closure without ultrasound guidance in high volume centers by expert and high-volume operators and after very careful TEE assessment before the procedure, we must acknowledge that during percutaneous closure of PFO, ultrasonographic monitoring should still be recommended in the majority of centers. TEE with the patient in deep sedation allows: a) accurate visualization and measurement of the septum and fossa ovalis in different views, b) monitoring device delivery, c) detection of complications. Intracardiac echography (ICE) is a reliable alternative option allowing a procedure without sedation therefore sparing costs of anesthesia, shortening procedure duration and catheterization laboratory occupancy, lowering risks and discomfort inherent with anesthesia and intubation. However the device is more expensive; requires a specific training, and a second vascular access. Although TTE can be an alternative in patients with selected cases, this method usually is not sufficient to allow accurate patient monitoring after the procedure.
	Through patient care Prophylactic antibiotics are administered before the beginning of the procedure. It is reasonable to start double antiplatelet therapy at least 12 hours before the procedure. In patients on oral anticoagulants, the anticoagulants are stopped, and when INR is less than 2, the patient is started on intravenous, unfractionated heparin. Anticoagulants are stopped before the procedure to allow a proper and controlled heparin regimen during the procedure. Patients are maintained on heparin throughout the procedure, maintaining an activated clotting time greater than 200 seconds. Conflicting evidence exist also regarding drug therapy following PFO closure. After the procedure, we suggest to treat patients with aspirin and clopidogrel for 3 to 6 months, and aspirin alone for an additional 6 months. Patients are also prescribed antibiotic prophylaxis against endocarditis in case of invasive procedures or surgical interventions during the first 6 months after the procedure. Patients who require oral anticoagulation for another condition resume warfarin as indicated for that condition, and do not take antiplatelet therapy while on anticoagulation unless otherwise indicated (e.g. some patients who have implantation of drug eluting stents may need “triple therapy” with oral anticoagulation, aspirin, and clopidogrel). The decision to continue therapy beyond 6 months is at the discretion of the heart-brain team, based on the evaluation of the residual shunt resulting from incomplete device endothelialization and on the relative weight of probability that further single factors (needing antiplatelet therapy) others than PFO may have come into play in the genesis of the index cerebral ischemic event(s). Older patients who have atherosclerotic disease (eg. coronary artery disease) may take antiplatelet therapy indefinitely.
RECOMMENDATIONS FOR FOLLOW UP EVALUATION	Follow up evaluation may include: (1) TTE at discharge and at 1, 3, 6 (if TEE not performed) and 12 months after the procedure. Thereafter, TTE evaluation annually (2) contrast-enhanced TCD or TTE with bubble study at 6 months after the procedure, (3) ECG and Holter ECG when clinically indicated (4) TEE when TCD or TTE with bubble study positive or when clinically indicated.

Table 6 - Summary of recommendations in the Italian position paper

Migraine

Current evidence on the efficacy of percutaneous closure of patent foramen ovale (PFO) for recurrent migraine is inadequate in quality and quantity. The evidence on safety shows a small incidence of well-recognised but sometimes serious adverse events, including device embolisation and device prolapse (each reported in less

than 1% of patients). Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research. Furthermore, patient selection for percutaneous closure of PFO for recurrent migraine should be carried out by a neurologist or other specialist in headache followed by an interventional cardiologist. Use of this procedure should be restricted to patients who are severely affected by recurrent, refractory migraine **G** (NICE, 2010).

Moreover, **M** (Butera, et al., 2010) infer that only in selected cases in which migraine with aura and a large PFO are associated with other disorders (atrial septal aneurysm, thrombophilia, peripheral venous thrombosis and/or previous history of paradoxical embolism) percutaneous PFO closure should be considered.

Decompression sickness in divers

High volume divers with decompression sickness or asymptomatic neurologic events who wish to continue diving may warrant PFO closure in appropriate centres **R** (Landzberg, et al., 2004).

However, current evidence on the efficacy of percutaneous closure of patent foramen ovale (PFO) for the secondary prevention of recurrent paradoxical embolism in divers is inadequate in quality and quantity, and the evidence on safety shows that there is a possibility of serious complications. Clinicians wishing to undertake percutaneous closure of PFO for the secondary prevention of recurrent paradoxical embolism in divers should thus ensure that patients understand the uncertainty about the procedure's efficacy and the possibility of complications, and that they accept alternative options which may include modifying their diving practice to reduce the risk of gas bubble formation **G** (NICE, 2010).

A0015 QUESITO: How is the disease/health condition currently being managed?⁵⁹

SOTTOCRITERIO: Utilisation

A0012 QUESITO: Describe the variations in use across countries/regions/settings, if any?⁶⁰

See QUESITO A0020

SOTTOCRITERIO: Authorisation & safety

I0015 QUESITO: Has the technology national/EU level authorisation?⁶¹

I0016 QUESITO: Does the technology need to be listed in a national/EU register?⁶²

I0017 QUESITO: Does the technology fulfil product safety requirements?⁶³

CE MARK

I0018 QUESITO: Does the technology fulfil the safety requirements?⁶⁴

CE MARK

SOTTOCRITERIO: Regulatory Status

A0020 QUESITO: Which approval status has the technology in other countries, or international authorities?⁶⁵

⁵⁹ FONTI INFORMATIVE: Surveys, utilisation reviews. If such information is lacking: Expert surveys / expert interviews.

⁶⁰ FONTI INFORMATIVE: Utilisation reviews, audits, studies on praxis-variation. Own primary analysis of: Disease register, procedure register, device register, administrative data (DRG, discharge databases, reimbursement claims database).

⁶¹ DESCRIZIONE: Patient safety as expressed in product safety is one domain of health care technology assessment which clearly falls under the mandate of the European Union.

⁶² DESCRIZIONE: A European database of medical devices (EUDAMED) is under construction.

⁶³ DESCRIZIONE: The implication of findings in the safety domain should be discussed against the relevant European or national legal frameworks to ensure patient safety from using the technology.

⁶⁴ DESCRIZIONE: Many novel health technologies may utilise human cells or tissue (so called advanced therapy medicinal products). These products must fulfil the safety requirements issued by EC Directive 2004/23/EC. FONTI INFORMATIVE: COM 567 (2005) final.

⁶⁵ DESCRIZIONE: Imaging devices may require approval. In addition, substances needed for the obtention of images may require additional approval (e.g. radiotracers). FONTI INFORMATIVE: Drugs: EMEA, FDA, National Authorities. Devices: CE-Approval, National Authorities. Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning Market-Approval.

There is a clear need for safety and performance to be established before new medical devices are approved but there is a fundamental tension between providing high-level clinical evidence and promoting innovation **R** (Fraser, et al., 2011).

EU

In Europe, the regulation of medical devices is the responsibility of the 27 Member States of the EU, each of which has its own national “competent authority”. Many national authorities have combined responsibilities for overseeing both drugs and devices, but there is no single, common European agency for assessing devices; the main role of the European Commission is advisory. For approval, manufacturers must satisfy the relevant ‘essential requirements’ of safety and performance but they do not always need to establish that their medical device has an impact on clinical outcomes, even if it is a completely new technology. If an equivalent device does exist, then a new device once approved can be marketed as an alternative without the manufacturer being required to prove in head-to-head comparisons that its clinical effectiveness is similar.

Any manufacturer wishing to obtain approval to market a new device in a medium- or high-risk group (classes IIa, IIb, III) must undergo a ‘conformity assessment procedure’ involving one or more Notified Bodies (NBs). The manufacturer must demonstrate safety and conformity with the legal requirements contained in the first annexes of the three directives. To do this, the manufacturer may refer to relevant technical standards such as those from the European Committee for Standardization (CEN) and the European Committee for Electrotechnical Standardization (CENELEC). In most instances, these mirror the standards from the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). Effective performance of the device for its intended purpose (as claimed by the manufacturer) needs to be demonstrated. The precise definition of the designated task of any device, therefore, is a key decision for each manufacturer. It can be argued that this process encourages the manufacturer to keep its claims for a device as simple as possible.

The clinical data used for CE marking may be a critical evaluation of the relevant scientific literature currently available relating to the design characteristics, intended purpose, safety, and performance of a device, when it is demonstrated to be equivalent to another device which already complies with relevant essential requirements and for which there are data. Alternatively, the manufacturer may present a critical evaluation of the results of all reported clinical investigations that have addressed residual safety concerns.

Most NBs are independent commercial organizations, and they are supported in part by the fees paid by device companies. Notified Bodies are designated, monitored, and audited by the competent authorities of the member state in which they are based. The NB may also visit the manufacturer to inspect the production process and quality control. If these tests are judged satisfactory, then the NB issues a certificate (which is valid for a maximum of 5 years before renewal) and the manufacturer can affix the CE mark. Thereafter, the device can be marketed throughout the EU. If a device needs to be removed from the market, it is the responsibility of the NB to suspend its certificate **R** (Fraser, et al., 2011).

USA

In the USA, the evaluation and approval of medical devices is the responsibility of the Food and Drug Administration (FDA) through its Center for Devices and Radiological Health (CDRH), which has a Division of Cardiovascular Devices. As in Europe, devices are categorized by risk into three classes, and higher levels of evidence including clinical evidence are required for approval of devices in Class III. In addition to internal regulatory review by FDA personnel, advice is often sought from external, independent experts through well-established Medical Devices Advisory Committees (including a Circulatory System Devices Advisory Panel), for example, for first-of-a-kind devices and for devices that are expected to have a broad impact on public health. This provides a transparent mechanism for public review of issues relating to the approval of complex devices. In general, regulatory reviews by the FDA incorporate more detailed technical standards and requirements for clinical evaluation of devices than occurs in Europe, and they are more rigorous **R** (Fraser, et al., 2011).

Patent foramen ovale (PFO)

At least 12 different PFO closure devices have received CE marking. Between 1999 and 2002, the FDA approved two PFO occluders as Humanitarian Use Devices, which means that a device has been designed to treat a disease that occurs in fewer than 4000 people in the USA per year. **The approved indication was limited to patients with recurrent cryptogenic stroke who had failed conventional drug therapy.** Approval was granted through the regulatory pathway for Humanitarian Device Exemption (HDE), and it was based upon clinical experience in <100 patients with each device. After approval of the HDEs, it became apparent that **many PFO**

occluders were being implanted off-label for patients with a first cryptogenic stroke who had not failed medical therapy. A systematic review published in 2004 reconfirmed the need for randomized studies R (Messé, et al., 2004), but recruitment continued to lag because "some physicians have concluded that the therapy is effective despite the lack of appropriate evidence". A re-analysis demonstrated that there were >4000 patients with cryptogenic stroke per year who might be candidates for PFO closure, and the two industry sponsors voluntarily withdraw their HDEs in 2006. Enrolment in studies remained slow despite more recommendations from FDA Advisory Panels and experts regarding the need for randomized trials, in 2007 and in 2009. Even though the two completed randomized trials (CLOSURE I and MIST) found PFO closure to be not better than medical treatment, unfortunately the procedure is already so 'established' that many clinicians remain unconvinced. No PFO closure device has been approved in the USA, but many devices continue to be implanted in Europe R (Fraser, et al., 2011).

As data are accumulating on the benefits of implanting PFO closure devices, it is also important to examine complications that might occur R (Verma, et al., 2011).

A0021 QUESITO: Has the technology been included in / excluded from the benefit basket of any country? How is the coverage of the technology across countries? (e.g. full-coverage, co-payments, coverage under special circumstances/conditional coverage?)⁶⁶

SOTTOCRITERIO: End-user

I0030 QUESITO: Is the use of the technology limited in legislation?⁶⁷

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Criterion C11 – Limitations of alternative technologies in use
Fonti: revisione della letteratura (linee guida cliniche, reviews in importanti riviste, reviews di Cochrane) Da fare: • Elencare le principali limitazioni degli interventi stabiliti nella Regione rispetto all'efficacia, sicurezza, outcomes riportati dai pazienti, popolazione eleggibile, convenienza, accettazione da parte del paziente • Dove possibile, riportare la proporzione di pazienti attualmente trattati • Citare nel testo le fonti più importanti inserendo la citazione a piè di pagina (<i>in Word 2010: Riferimenti / Inserisci nota a piè di pagina</i>) Da non fare: • Non riportare le limitazioni dovute ai costi (verranno discusse nel punto E1) • Non discutere se gli interventi proposti possono avere limitazioni, o comparare la tecnologia proposta con quelle correnti

SOTTOCRITERIO: Current Management of the Condition

A0018 QUESITO: What are the other evidence-based alternatives to the current technology, if any?⁶⁸

Long-term anticoagulation or antiplatelet therapy, surgical PFO closure, besides percutaneous transcatheter closure of the PFO have been proposed as therapeutic options. Medical therapy and surgical closure are associated with a significant morbidity and mixed results regarding stroke prevention. Transcatheter closure of PFO offers the advantages of closure of the defect without the disadvantages of open-heart surgery, since it is a minimally invasive procedure which can be performed with high success and low morbidity. With respect to secondary prevention of recurrent embolic events, percutaneous PFO closure appears to be clinically at least as effective as medical treatment R (Meier, et al., 2012).

Regarding medical therapy, the results of CLOSURE I underline higher adverse event rates related to death and nervous system disorder (respectively 0,9% vs 0,5% closure group and 3,5% vs 1,5% closure group).

In other comparative studies the risk underlined with medical therapy is for higher major bleeding, compared to percutaneous closure, furthermore warfarin is considered to be better than antiplatelet and comparable to surgical closure in terms of recurrence rate of neurological events.

However, the mortality and morbidity risks from surgery are immediate at the time of therapy SM (Homma, et al., 2002).

⁶⁶ DESCRIZIONE: Are there co-payments, to what extent? FONTI INFORMATIVE: Lists of benefits / services of the National Health Services / Sickness Funds, inquiry of technical officers from MoH. Manufacturers. Literature on Benefit Basket (Comparative policy studies).

⁶⁷ DESCRIZIONE: Some countries may have restricted the use of some diagnostic technologies.

⁶⁸ FONTI INFORMATIVE: Clinical guidelines, recommendations, systematic reviews.

When comparing drugs used in medical therapy, both observational and randomized data are consistent and suggest that, despite the increased risk of associated hemorrhage, anticoagulants are superior to antiplatelets for secondary prevention of stroke recurrence (IR ratio=0,42; 95% CI, 0,18–0,98), although the strength of evidence would be considered low to moderate by conventional criteria for assessing the overall strength of a body of evidence **R** (Kitsios, et al., 2012) **M** (Orgera, et al., 2001).

More specifically, although medical treatment lacks the risk of interventional procedures, it is associated with other adverse effects, most notably an increased risk of bleeding, as it has been reported previously. Thus, major bleeding amounted to 1,5–2,2 per 100 patient-years in the prospective PICSS **SM** (Homma, et al., 2002) and its subanalysis, the Warfarin-Aspirin Recurrent Stroke Study (WARSS), with no significant differences between acetylsalicylic acid and oral anticoagulation. Treatment with acetylsalicylic acid has been found insufficient in patients with PFO and associated ASA. Another important limitation of medical treatment is lack of compliance **R** (Meier, et al., 2012).

A0017 QUESITO: What are the differences in the management for different stages of disease, if any?⁶⁹

SOTTOCRITERIO: Target Condition

A0010 QUESITO: How long is the waiting time for diagnosis and/or treatment of the specific disease?⁷⁰

⁶⁹ DESCRIZIONE: Identification of practice variations which point out differences in the quality of health care. FONTI INFORMATIVE: Surveys, utilisation reviews, clinical guidelines, recommendations. If such information is lacking: Expert surveys / expert interviews .

⁷⁰ DESCRIZIONE: This refers to the time between presentation and final diagnosis and the time between presentation and initiation of therapy. These can be described as “provider delay”. These times reflect mainly quality shortcomings but they may be also an indication of the lack of good diagnostic test. FONTI INFORMATIVE: Systematic reviews of epidemiological studies such as cross-sectional studies, cohort studies, etc.

Dimension D5: Economic and Financial Impact

Criterion C12 – Financial Impact on Health system

Fonti: spesso dati dell'azienda (piano sanitario, produttore)

Da fare:

- Mettere in tabella i dati sui costi per paziente per la tecnologia e i comparatori (prezzo della tecnologia, frequenza/durata dell'intervento, stima annuale, implementazione dei costi per equipaggiamenti, etc)
- Indicare il tipo di modello usato (basato sulla domanda, epidemiologici), costi inclusi (tasse, mark-up, costo di somministrazione delle iniezioni, etc) & principali ipotesi
- Mettere in tabella l'impatto economico del progetto (numero di pazienti, costo a carico della sanità pubblica, aumento dei costi [se va a sostituire una tecnologia già presente])
- Fornire una spiegazione sulla differenza tra il piano sanitario e il costo incrementale
- Fornire i dati più importanti che possono far variare in modo significativo la stima di spesa (ad es. farmaci bioequivalenti se non sono inclusi nel modello)

SOTTOCRITERIO: Resource utilization

E0001 QUESITO: What types of resources are used when delivering the assessed technology and its comparators (resource use identification)?⁷¹

E0002 QUESITO: What amounts of resources are used when delivering the assessed technology and its comparators (resource use measurement)?⁷²

As a recent review reports, the incidence of stroke appears to be increasing, and the associated economic costs are staggering. The 2008 estimated direct and indirect cost of stroke in US is \$65.5 billion, with a mean per capita lifetime cost of \$140 048 R (O'Gara, et al., 2009).

A Swedish analysis reports that the costs of AVK (or anticoagulants) are only marginally affected as AVK is given to patients before discussing about closure with the clinician. The majority of patients considered to have cryptogenic stroke due to PFO receive lifelong treatment with ASA, whether catheter-based closure is carried out or not, so this cost is not affected. Thus most of the cost derives from relapse: previous HTA reports indicated healthcare costs for a stroke to an average of 730.000 SEK (~73.000 €). If further research would confirm/strengthen the results of recurrence of 5% per year without catheter closure versus 1% after catheter closure, it would mean that 35 patients referred for PFO closure, for instance, end up with costing 1.3 million per year in terms of stroke recurrence if they don't undergo PFO closure. Costs vary depending on material consumption, anyhow total costs are between 98 to 118.000 SEK per event, which include all expenses, excluding sick-leave for 3-4 days. The cost of the approximately 35 cases per year, for instance, is about four million a year R (Dellborg, et al., 2010).

In a first exploratory analysis of hospital discharge forms of the Lombardy Region Data Warehouse from 2003 to 2011, reported the attribution of different reimbursement tariffs over the years and the use of a different codification for the procedure of patent foramen ovale closure. Until the 31st August 2004, the reimbursement was equal to the 80% (4.778 €) of the total value of the prosthesis (5.972 €), equal to 100% of the total value (5.972 €) from the 1st September 2004 to the 28th February 2007, and from then on the evaluation for reimbursement is 5.873 €. It's important to add that the total cost of the procedure, which depends on the diagnostic instrumentation, amounts around 10.000-15.000 €, including the prosthesis, however direct costs are difficult to associate and calculate (Barbieri, 2012).

SOTTOCRITERIO: Unit costs

⁷¹ DESCRIZIONE: In order to do an economic evaluation all types of resource utilization must be identified. The study perspective determines what kinds of resource utilization must be identified. A societal perspective implies identifying all kinds of resource utilization irrespective of who pays for the resources. If a health care provider perspective is applied, then resource utilization paid for by the patient is not relevant. FONTI INFORMATIVE: Health care registers, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies.

⁷² DESCRIZIONE: For all types of resource utilization the amounts of resources used when delivering the assessed technology as well as when delivering the comparator technologies must be measured. FONTI INFORMATIVE: Health care registers, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies.

E0003 QUESITO: What are the unit costs of the resources used when delivering the assessed technology and its comparators?⁷³

SOTTOCRITERIO: Investments and tools required to use the technology

B0007 QUESITO: What material investments are needed to use the technology?⁷⁴

B0009 QUESITO: What equipment and supplies are needed to use the technology?⁷⁵

B0010 QUESITO: What kind of data and records are needed to monitor the use the technology?⁷⁶

B0011 QUESITO: What kind of registers is needed to monitor the use the technology?⁷⁷

SOTTOCRITERIO: Structure

G0007 QUESITO: What is the likely budget impact of the implementation of the technology for the payers (e.g. government)?⁷⁸

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Criterion C13 – Cost-effectiveness

Fonti: revisione della letteratura, dati dell'azienda (produttore o gestione sanitaria es. ASL, AO, Fondazione)

Da fare:

- Fornire sufficienti informazioni per comprendere il disegno e i risultati della valutazione economica paese-specifica.
 - Popolazione, tecnologia, comparatori, prospettiva di analisi, modello tipo e orizzonte temporale, efficacia/effectiveness dati utilizzati, dati utilizzati per riportare gli outcome dei pazienti, caratteristiche dei modelli chiave
 - Presentare l'incremento del costo-efficacia e le analisi di sensibilità.
- Se sono disponibili altre valutazioni con altre caratteristiche, fornire l'ICER solo per fornire un range.

SOTTOCRITERIO: Outcomes

E0005 QUESITO: What are the incremental effects of the technology relative to its comparator(s)?⁷⁹

⁷³ DESCRIZIONE: Ideally unit cost estimates should be (proxies for) opportunity costs. By the opportunity cost is understood the (lost) health gains that could have been achieved from an alternative technology, which, however, cannot be introduced or retained, because the resources e.g. manpower, are used on the new technology. Market prices are often used as proxies for opportunity costs. FONTI INFORMATIVE: Market prices, companies, hospital accounting systems, reimbursement databases, micro level costing studies/ABC-costing studies.

⁷⁴ DESCRIZIONE: Devices, machinery, computer programs, etc. Those parts of the technology that need to be purchased (and often installed) by an organization in order to use the technology. Includes need for back-up investment to cover for breakdowns in use. FONTI INFORMATIVE: Manufacturer, applicability studies, clinical experts, user information. National or local judgement.

⁷⁵ DESCRIZIONE: Syringes, needles, medicines, fluids, bandages etc. All disposable items necessary for using the technology. FONTI INFORMATIVE: Manufacturer, applicability studies, clinical experts, user information. National or local judgement.

⁷⁶ DESCRIZIONE: What kind of data needs to be collected about the use of this technology regarding care processes, professionals involved, patients and their health outcomes? FONTI INFORMATIVE: Clinical experts, administrative experts, legislation. National or local judgement.

⁷⁷ DESCRIZIONE: Are there existing registries that should be used, or should a registry be established, to collect the necessary data? FONTI INFORMATIVE: Clinical experts, administrative experts, legislation. National or local judgement.

⁷⁸ DESCRIZIONE: When a new technology is introduced, the question about reimbursement quickly arises. Whenever a technology is reimbursed, there will be an impact on the health care budget. Budget impact analysis examines the likely impact of the reimbursement of a new technology on financial outlays from the perspective of the payers (e.g. government). FONTI INFORMATIVE: Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods.

⁷⁹ DESCRIZIONE: The calculation of an incremental cost-effectiveness ratio requires the estimation of the incremental effectiveness/utility/benefit of a technology relative to its comparator(s). FONTI INFORMATIVE: Estimation of the incremental effects can be based on information provided in the effectiveness domain (e.g. mortality data). Additional information collection may be needed (e.g. on health-related quality of life indices). The incremental effectiveness may result from an economic model, where inputs from the effectiveness domain are used (amongst others).

SOTTOCRITERIO: Cost-effectiveness

E0006 QUESITO: What is the incremental cost-effectiveness ratio?⁸⁰

Regarding these typologies of analyses, few data are available at the moment. Even though caution should be taken with extrapolation of results to other countries with different economies, since differences in costs of interventions, variations in payment threshold, and preferences of doctors and patients might affect conclusions, a model of cost-effectiveness analysis for management of patients with patent foramen ovale has been proposed by an Argentine study R (Arias, et al., 2011).

A cost-utility analysis was conducted based on a decision tree with a time horizon of 4 years considering three strategies: aspirin (ASA), anticoagulants (AC) or percutaneous device closure of the PFO. The benefits were expressed in QALYs. A payment threshold of ARS \$28.000 (Argentine pesos) was established and a sensitivity analysis was performed.

Model assumptions:

The event was defined at the occurrence of stroke or transient ischemic attack (TIA) with a 4 year time horizon. Recurrence was considered to occur in the first year, so neither costs nor QALYs associated with it were discounted. TIA utility ratio was similar to that of “minor” stroke reported in the literature. When the data were expressed in more than one year in the literature, it was considered that the rate of events was similar in each yearly period.

Decision rules and sensitivity analysis:

The willingness to pay that was set to accept an intervention as “useful-cost” was 1 GDP per capita, equivalent to an incremental cost-utility ratio of ARS \$28.000 for each extra QALY gained.

Alternative strategies:

- Aspirin treatment: Patients were treated with aspirin 300 mg/day, they visited their cardiologist twice a year, and no screenings were performed.
- Acenocumarol treatment: Patients were treated with acenocumarol as determined by lab tests. They visited their cardiologist twice a year, and their hematologist, once a month. No screenings were performed, except for the monthly anticoagulation monitoring.
- Percutaneous device closure of PFO: After the intervention, patients were treated with aspirin 300 mg/day. They were controlled by the cardiologist every 3 months.

Benefits utilized:

Since the recurrence endpoint was stroke or TIA, an average between the mean QALY of such revision for ‘minor’ and ‘major’ stroke was obtained. A zero QALY value was considered for mortality rate.

Costs and discount utilized:

Costs were expressed in Argentine pesos (ARS), and the **currency exchange was 1 dollar = 4 pesos in October 2010**. To elicit the mean cost per stroke (recurrence), it was found that one third of the patients presented low costs (ARS \$9.000), since they only required hospitalization, imaging studies, anticoagulant and/or antiplatelet therapy, and post-stroke rehab through kinesiology; another third of the patients required interventions with longer hospitalization periods and involved digital angiographies at a mean cost of ARS \$12.000; finally, a third group required open surgeries or percutaneous interventions at a mean cost of ARS \$18.000. This represents an estimated mean cost of around ARS \$12.987 per stroke. The table below shows in detail the main costs used, as well as the sensitivity analysis range.

⁸⁰ DESCRIZIONE: The result of the economic analysis will most often be an incremental cost-effectiveness ratio eg. costs/QALY if quality-adjusted life years is used as the main outcome indicator. The incremental cost-effectiveness ratio does not in itself determine that a technology is desirable. Decision makers need – implicitly or explicitly – to weigh the benefits of a technology against the costs. The concept of a cost-effectiveness threshold is one way of expressing decision-makers willingness-to-pay for health benefits. If other types of economic evaluation is chosen, eg. cost benefit analysis, other types of measures are used to express results of the analysis, but most current economic analysis within HTA's are done within the cost-effectiveness/cost-utility framework. FONTI INFORMATIVE: Sources of data used are specified under relevant issues under domains safety, effectiveness and costs. The ICER estimate might result from the economic model, using inputs from the safety and effectiveness domain.

A 3% discount rate was used both for costs and benefits. In the sensitivity analysis, a range between 0% and 10% was considered.

Variable	Central estimation	Range
Probabilities (%)		
Aspirin mortality rate	3.9	3-5
Anticoagulation mortality rate	2.5	1-4
Device closure mortality rate	0.7	0.2-1.3
Device closure success rate	83	75-95
Recurrence with aspirin	25.Re4	15-35
Recurrence with anticoagulation	19.3	15-25
Recurrence after device closure (unsuccessful)	7.8	4-12
Recurrence after device closure (successful)	6.4	2-10
Costs (ARS \$)		
Annual cost of aspirin therapy	196	171-221
Annual cost of anticoagulation therapy	740	550-900
Annual cost of device closure	34,000	30,000-38,000
Cost of recurrence	12,987	10,000-17,000
QALYS		
Minor stroke	0.72	± 10%
Major stroke	0.41	± 10%
Minor and major stroke	0.57	± 10%
ASA therapy	0.98	± 10%
AC therapy	0.92	± 10%
Treatment with closure device	0.95	± 10%

Table 7 - Probabilities, costs and QALYs utilized. Central estimation and range for sensitivity analysis

Results (Table 8):

Acenocumarol treatment produced an incremental cost of ARS \$1.315 with respect to ASA, but benefits were low (incremental QALY -0,063). Therefore, anticoagulation strategy was considered to be dominated by aspirin. Compared with aspirin treatment, percutaneous device closure showed an incremental cost of ARS \$32.261 and an incremental benefit of 0,359 QALY; it represents an incremental cost-utility ratio of ARS \$89.876 per each extra QALY gained.

Strategy	Cost	Incremental cost	Benefit (QALYs)	Incremental benefit	Mean C-U	Incremental C-U
ASA	3,891	–	3.212	–	1,211	–
AC	5,206	1,315	3.149	-0.063	1,653	DOMINATED
Device	36,152	32,261	3.571	0.359	10,124	89,876

Table 8 - Incremental cost-utility ratio

Conclusion:

This model shows that, according to the payment threshold of ARS \$28.000/QALY recommended by the World Bank for economies in Argentina, the device strategy resulted in cost-ineffective. Anticoagulation strategy has been dominated by ASA, because AC was more expensive and less effective. These results were maintained after the sensitivity analysis, except when the probability of recurrence with ASA increased to 35% R (Arias, et al., 2011).

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Criterion C14 – Impact on other spending

(indirect costs: hospitalization, disability, etc)

Fonti: revisione della letteratura, valutazioni economiche (vedere 4e.2 Costo-efficacia della tecnologia)

Da fare:

- Mettere in tabella l'impatto della tecnologia e i comparatori su altre spese (esclusi i costi della tecnologia), come ospedalizzazione, eventi avversi, disabilità, perdita di produttività.
- Stimare il totale impatto della tecnologia e dei competitori e calcolare la differenza assoluta (incremento), se possibile.
- Spiegare il motivo per cui la tecnologia porti/non porti un risparmio (se non è ovvio dalla tabella)
- Citare nel testo le fonti più importanti inserendo la citazione a piè di pagina (*in Word 2010: Riferimenti / Inserisci nota a piè di pagina*)

Da non fare:

- Non riportare i dati su costi della tecnologia e dei competitori (presenti in 4E.1; ad es. costo per l'acquisto dei farmaci, aumento dei costi dell'equipaggiamento)
- Non includere l'incremento potenziale dei costi della tecnologia; dovrebbe essere presente in 4E.1 (Impatto sulla spesa sanitaria).

SOTTOCRITERIO: Indirect Costs

E0004 QUESITO: What is the impact of the technology on indirect costs?⁸¹

SOTTOCRITERIO: Ownership & liability

I0020 QUESITO: Does the introduction of the technology presume some additional licensing fees to be paid?⁸²

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Criterion C15 – Impact on efficiency (cost-opportunity)

Da fare: citare nel testo le fonti più importanti inserendo la citazione a piè di pagina.

Le conclusioni della valutazione dovrebbero riportare adeguate misure di sintesi, appropriate al tipo di analisi identificata e/o condotta (ad esempio, per le analisi costo-utilità, i rapporti incrementali tra le differenze di costo e di efficacia, espresse in QALYs – RICE) e ogni altra misura utile alla stima ed alla interpretazione del rapporto di costo-opportunità della tecnologia in oggetto.

Quando l'analisi ha considerato più di un'alternativa di confronto, dovrebbero essere separatamente presentate le misure di sintesi relative a tutte le alternative prese in considerazione. L'entità degli effetti su efficacia e su costi dovrebbe essere riportata anche qualora la tecnologia esaminata risulti meno efficace e più costosa delle alternative. Le stime dovrebbero riportare misure di posizione (medie, mediane, ecc.) e misure di dispersione (deviazioni standard, intervalli di confidenza ecc.), dovrebbero essere affiancate da analisi delle incertezze e della generalizzabilità delle conclusioni delle valutazioni clinico-economiche alla generalità dei pazienti (sezione O) o a particolari sottogruppi di pazienti (sezione P).

Obiettivo generale delle valutazioni è documentare quegli investimenti sanitari potenzialmente in grado di massimizzare i benefici (guadagni di salute) ottenibili con l'accorto uso delle risorse sanitarie effettivamente disponibili. A questo fine è raccomandata la identificazione di miglioramenti di salute non ambigui effettivamente ottenibili con le risorse impiegate nella pratica.

In questo caso i benefici di salute incrementali che si stima siano raggiungibili con l'applicazione delle strategie oggetto dell'esame sono comparati con i benefici di salute attualmente ottenuti con quella combinazione di altre tecnologie che è necessario dismettere al fine di generare sufficienti risorse per finanziare le strategie innovative. Quando, e solo quando, i benefici di salute incrementali delle strategie oggetto di esame eccedono i benefici di salute attuali delle altre tecnologie, si identifica una occasione di miglioramento dell'efficienza allocativa. In caso opposto la tecnologia in esame, benché proposta come innovativa, non è verificata come tale.

SOTTOCRITERIO: Major life areas

H0003 QUESITO: What kind of support and resources are needed or might be released as the technology is put to use?⁸³

⁸¹ DESCRIZIONE: Indirect costs include costs to society of lost production. This can be due to patient's temporary absence from work due to illness, reduced working capacity due to illness and disablement, or lost production due to an early death. FONTI INFORMATIVE: Different registers e.g. register on sick leave, sickness allowance, patient administration systems/clinical databases, earlier studies, cost diaries.

⁸² DESCRIZIONE: As novel technologies build up on existing knowledge, the use of the technology may involve the payment of some additional fees to additional patent holders etc. In principle, the manufacturer should be able to clarify this to the health care unit/health care system in question. FONTI INFORMATIVE: Manufacturer, patent data bases.

⁸³ DESCRIZIONE: This issue is about any kind of support and resources (practical, physical, emotional, personal social, nurturing, financial etc.) that need to be mobilized, and organized - or might be released - in order for the patient to use the technology with satisfactory results. It covers all arrangements or adjustments that may be needed in the major life areas

H0004 QUESITO: What kinds of changes does the use of the technology generate in the patient's role in the major life areas?⁸⁴

H0005 QUESITO: What kind of changes does the implementation and use of the technology mean for the patients physical and psychological functioning in his or her major life areas?⁸⁵

SOTTOCRITERIO: Structure

G0006 QUESITO: What kinds of investments are needed (material or premises)?⁸⁶

G0005 QUESITO: What consequences the implementation of the new technology will have in respect of decentralisation or centralisation?⁸⁷

(e.g. alteration of special tasks, working time, adjustments in the physical environment, emotional support). FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

⁸⁴ DESCRIZIONE: This issue is about the patient's social roles and ability to manage and maintain relations with other people in a socially appropriate manner in major life areas. FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

⁸⁵ DESCRIZIONE: This issue is about the physical and psychological consequences the use of the technology may generate in the patient's main life areas e.g. on person's body functions and structures, activities on daily living, or performance at work, school, home or leisure time. This issue covers whether, from a patient perspective, the technology leads to improvements or harms (a cross reference to effectiveness, safety domain issues), or generates any other unexpected effects on functioning. FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

⁸⁶ DESCRIZIONE: The new technology could require many changes in the organisation e.g. premises must be according to the directions of the manufacturer. This could be very costly for the organisation. High costs of the new technology can influence the decision of purchasing the new technology. It is important to know which organisation(s) participate in the investments of a new technology and to what extent the other organisations take part in the running costs. FONTI INFORMATIVE: Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods. Information from manufacturers.

⁸⁷ DESCRIZIONE: The location of use of the technology (primary - secondary - tertiary care) could vary between different countries depending on the system of organisational systems. (De)centralisation could have some economical and qualitative benefits. Centralisation could make a new technology more difficult to access. E.e. expensive technologies are centralized to tertiary care units. FONTI INFORMATIVE: Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods.

Dimension D6: Equity

Criterion C16 – Impact on equity and accessibility

Fonti: Letteratura, opinione di esperti, opinione degli stakeholder

Da fare: La tecnologia può intaccare la dignità umana?

SOTTOCRITERIO: Justice and Equity

F0012 QUESITO: What are the consequences of implementing / not implementing the technology on justice in the health care system? Are principles of fairness, justness and solidarity respected?⁸⁸ (INTERVENTION)

F0013 QUESITO: How are technologies presenting with relevantly similar (ethical) problems treated in health care system?⁸⁹

SOTTOCRITERIO: Equality in health care

I0011 QUESITO: Is the technology equally accessible to all needing members in a given society?⁹⁰

I0012 QUESITO: Is the technology subsidized by the society?⁹¹

I0013 QUESITO: Is there a wide variation in the acceptability of the technology across Europe?⁹²

I0014 QUESITO: Is health-care tourism expected from/to other European countries?⁹³

SOTTOCRITERIO: Regulation of the market

I0025 QUESITO: Is the marketing of the technology to the patients restricted?⁹⁴

(Nota: la regolamentazione è sufficiente a garantire l'utilizzo appropriato e prevenire un eventuale abuso della tecnologia considerata?)

⁸⁸ DESCRIZIONE: A new intervention may require reallocation of human resources, funding and training. A large reallocation of resources may seriously jeopardize other patient groups (e.g. new technology that requires human resources in acute care). How this reallocation affects the existing health care system has to be studied for all stakeholders? Can the technology be applied in a way that there is equal access to those in equal need? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, employment, insurance) prevent access? Are specific safeguards needed? How will possible caregivers' burden and well-being be influenced? Potential inequalities and discrimination should be justified. FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

⁸⁹ DESCRIZIONE: Clearly presenting how relevantly similar technologies are treated in a health care system may help to adopt coherent and just health policies, either by applying past precedents to current cases, or showing that past cases need reconsideration. Similarity is to be defined individually for each technology. The idea is to concentrate only on the similarities relevant for solving the ethical problems found important for the current HTA project. The similarity may be, for example, of medical, technological, economical, ethical, social, organisational or legal nature. FONTI INFORMATIVE: Literature search. Expert opinion.

⁹⁰ DESCRIZIONE: This topic operates both at national and international level. In general, equality in health care is spoken out in the EU Charter of Fundamental Rights and it is also one of the central principles of the Biomedicine Convention. In many Constitutions equality of citizens covers also access to health care.

⁹¹ DESCRIZIONE: Governmental interventions or the lack of them may affect to the expected number of patients.

⁹² DESCRIZIONE: Varying legal regimes may lead to health-care tourism across the borders, especially if the technology in question is controversial. FONTI INFORMATIVE: Europe-wide legal comparison.

⁹³ DESCRIZIONE: Varying legal regimes may lead to health-care tourism across the borders. FONTI INFORMATIVE: C-158/96 (ECJ), C-372/04 (ECJ), Europe-wide legal comparison.

⁹⁴ DESCRIZIONE: As health care technology is essential to everyone at some point in their lives, the way by which it can be marketed to consumers may be regulated. FONTI INFORMATIVE: T-179/00 (ECJ).

Dimension D7: Social and Ethical Impact

Criterion C17 – Coherence with National regional planning

Fonti:

Da fare: citare nel testo le leggi, delibere, decreti e altra normativa e regolamentazione pertinente, inserendo la citazione a piè di pagina

SOTTOCRITERIO: Regulation of the market

I0023 QUESITO: Is the technology subject to acquisition regulation?⁹⁵

I0024 QUESITO: Is the technology subject to price control?⁹⁶

SOTTOCRITERIO: End-user

I0031 QUESITO: Who is the intended end-user of the technology?⁹⁷

I0032 QUESITO: Is the health care personnel using the technology according the professional standards?⁹⁸

There are potential ethical problems in the use of a (costly) technology with lack of efficiency and with uncertain long-term effects also in terms of patient safety. Using a promising technology with potential great value for a relatively large group of young patients with a high risk of recurring stroke is ethically difficult in a case where the disease is costly to the community R (Dellborg, et al., 2010).

SOTTOCRITERIO: Privacy of the patient

I0009 QUESITO: Can the access to the patient data secured properly?⁹⁹

I0010 QUESITO: What levels of access to which kind of patient information exist in the chain of care?¹⁰⁰

⁹⁵ DESCRIZIONE: Expensive technology is subject to acquisition regulation.

⁹⁶ DESCRIZIONE: As health care technology is essential to everyone at some point in their lives, its pricing may be regulated.
FONTI INFORMATIVE: C-317/05 (ECJ), C-283/03 (ECJ).

⁹⁷ DESCRIZIONE: Different requirements may apply depending on the answer. E.g. consumer Information, CE-marks, easiness of use, exactness of the results etc. are to be evaluated differently if the technology is intended to laymen's use.
FONTI INFORMATIVE: "In vitro diag. directive 98/79/EC; " Council of Europe Gen testing protocol 2008.

⁹⁸ DESCRIZIONE: Health care personnel are obliged to follow professional standards and apply methods that are generally approved. When considering professional liability towards patients it is important that they know limits and possibilities of diagnostical methods.

⁹⁹ DESCRIZIONE: At the era of computer-based patient records it is crucial that the health care unit has taken appropriate measures to secure the patient databases. Negligence may lead to liability.

¹⁰⁰ DESCRIZIONE: During the therapeutic process many people may either need to get access or semi-accidentally get access to the personal medical data of patients. The delicacy of the information depends on the technology in question. Health care unit must be organised so that it minimises the number of people having access to patient data. Also other measures to minimise the risk of information leakage from health care unit must be taken.

Criterion C18 – Impact on healthcare needs

Fonti: letteratura, opinione di esperti

Da fare: citare nel testo le fonti più importanti inserendo la citazione a piè di pagina

Domande:

- La tecnologia è innovativa? E' un'aggiunta, una modifica o una sostituzione del modello standard?
- L'uso della tecnologia può modificare l'autonomia del paziente?
- La tecnologia è utilizzata per pazienti particolarmente vulnerabili?
- La tecnologia può comportare modifiche del rischio di cui il paziente necessita di essere informato?
- La tecnologia può modificare i valori professionali, etici o i ruoli tradizionali?
- E' rispettata la sussidiarietà?
- Quali sono le tecnologie che presentano simili problemi etici nel sistema sanitario?

SOTTOCRITERIO: Principal questions about the ethical aspects of technology

F0001 QUESITO: Is the technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or a replacement of a standard?¹⁰¹

F0002 QUESITO: Can the technology challenge religious, cultural or moral convictions or beliefs of some groups or change current social arrangements?¹⁰²

NO

SOTTOCRITERIO: Rights

F0014 QUESITO: Does the implementation or use of the technology affect the realization of basic human rights?¹⁰³

NO

SOTTOCRITERIO: Human integrity

QUESITO: Does the implementation or use of the technology affect human integrity?¹⁰⁴

NO

¹⁰¹ DESCRIZIONE: The consequences of totally new models of care are likely to be more difficult to predict than the consequences of replacing an old technology (for individual values, attitudes and expectations as well as for health care systems). Novel, innovative treatment modes may require extra emphasis on ethical analysis, although the literature and research base on the topic may be narrow. FONTI INFORMATIVE: Literature search. Expert opinion.

¹⁰² DESCRIZIONE: It is important to identify those groups within the society for whom the use of the technology may pose serious challenges due to their beliefs, convictions or current social arrangements (e.g. need of blood transfusion adjunct to the use of the technology, contraception). Identification of these conflicts and finding other, acceptable possibilities to treat the condition in these groups is important. Identifying the conceptions behind the beliefs and values may help put them in perspective, when considering the overall acceptability of the technology. Technology may also change generally accepted social arrangements by challenging traditional conceptions (e.g. assisted reproductive technologies have separated the concept of genetic, biological and social motherhood). FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

¹⁰³ DESCRIZIONE: Human rights exist both in ethics and legislation, most notably in the United Nations declarations and related statements, like the European Council Biomedicine convention. Basic human rights are universal and consider the most important goods, protections and freedoms. Classes of rights are civil and political rights, social rights, minority and group rights and environmental rights. For HTA, perhaps the most relevant are the rights to equality, non-discrimination, safety, adequate standard of living and health care. For example: -Right to life, liberty and security of person. -Right to a standard of living adequate for the health and well-being of himself and of his family, including medical care and necessary social services, and the right to security in the event of sickness, disability or old age. -Right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. FONTI INFORMATIVE: Literature search. Law, rules and regulations. Expert opinion. Stakeholder hearing.

¹⁰⁴ DESCRIZIONE: "Technology can challenge human integrity by preventing (or even tempting) people (patients or professionals) to live according to their moral convictions, preferences or commitments. This is especially important for vulnerable patient groups. Integrity can also be seen as a coherent image or identity of oneself. Thus, for example, prenatal diagnostics might challenge the integrity of people who value new life as gift; cochlear implants are problematic for those, who do not see deafness as a disability. Institutions that discourage honesty or ethical conduct more generally are detrimental to integrity (for example, systems where lying about ones health state might lead to better treatment than being honest)." FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

SOTTOCRITERIO: Beneficence/nonmaleficence

F0010 QUESITO: What are the benefits and harms for patients, and what is the balance between the benefits and harms when implementing and when not implementing the technology? Who will balance the risks and benefits in practice and how?¹⁰⁵

Surgical closure of the PFO provides an alternative to lifelong antiplatelet or anticoagulation therapy. Surgical treatment can potentially permanently close the interatrial defect, eliminating the need for medical therapy. The major disadvantage of surgical closure is that it requires thoracotomy and cardiopulmonary bypass. Percutaneous endovascular PFO closure theoretically offers benefit of eradication of the right-to-left shunt without the risks associated with surgical intervention; nevertheless, complications can also occur **R** (Anamnart, et al., 2011).

Even though there is no scientific proof that PFO closure is preferable to medical treatment, patients who have had a stroke are anxious that they will suffer another event and often prefer the certainty of an intervention over medical therapy **R** (Tobis, et al., 2012).

As it was previously shown, many studies suggest that the recurrent stroke/TIA rates after PFO device closure are comparable to rates from studies of recurrent events in patients with PFO and cryptogenic stroke treated with various regimens of medical treatment; however, PFO closure has not yet been proved superior to medical treatments. Despite enthusiasm for eliminating a theoretical cause of cryptogenic stroke by PFO closure, patients deserve a clear presentation of the uncertain benefits of closing the PFO before proceeding. In discussions with patients, it has to be emphasized that the procedure would eliminate only one potential possible cause for stroke **R** (Kutty, et al., 2012).

SOTTOCRITERIO: Human Dignity

F0009 QUESITO: Does the implementation or use of the technology affect human dignity?¹⁰⁶

NO

SOTTOCRITERIO: Autonomy

F0004 QUESITO: Does the implementation or use of the technology challenge patient autonomy?¹⁰⁷

F0005 QUESITO: Is the technology used for patients/people that are especially vulnerable?¹⁰⁸

¹⁰⁵ DESCRIZIONE: The decision to implement new diagnostic technology requires careful decision on the balance between benefit and harm, cost-effectiveness, reallocation of resources etc. When this decision has been made on the system level, the decision on individual patient level rests on both the professional who offers the technology and the patient who autonomously accepts the use of technology in her/his situation. The individual decision has to be based on objective information on possible benefit and risks. Risks are only justified to the extent they are needed to create benefits. If not proven otherwise, the individual patient is generally to be seen as the best judge of risks and benefits for her/himself. FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

¹⁰⁶ DESCRIZIONE: Especially technologies that are applied for persons with reduced autonomy may violate a person's dignity (children, mentally impaired, severely ill), i.e. challenge the idea that all human beings have intrinsic moral value, and should thus not be seen as means to others ends. FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

¹⁰⁷ DESCRIZIONE: Patients have in most cases a right to autonomy, i.e. right to be self-governing agents. This requires the right to decide about things of importance to oneself on one hand, but also relevant information and a capability to understand the information, consider it in relation to personal values and decide accordingly. Thus, technologies and health systems may interfere with patient's right to autonomy directly or indirectly by influencing the decisional capacity. For example, a technology that does not allow itself to be understandably explained to the patient (e.g. gene therapy for dementia) is potentially problematic, as are treatments that require patients to behave in a certain way (e.g. liver transplants given conditional to not drinking). FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

¹⁰⁸ DESCRIZIONE: The right and justification to use the technology for persons who are vulnerable (critically ill or have otherwise reduced decision making capacity, like children, mentally retarded, patients that have due to their illness/state limited decision making capacity, pregnant women etc) has to be clarified. Who has the right to balance the benefit against possible harm in these situations? On what grounds can these decisions be made? Is the technology so valuable, as to justify its use on people who cannot give informed consent to it? FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

F0006 QUESITO: Can the technology entail special challenges/risk that the patient/person needs to be informed of?¹⁰⁹

F0007 QUESITO: Does the implementation challenge or change professional values, ethics or traditional roles?¹¹⁰

I0002 QUESITO: Can patients understand the implications of using/not using the technology?¹¹¹

I0003 QUESITO: Are there relevant optional technologies that future patients should be allowed to consider?¹¹²

I0004 QUESITO: Is it possible to give future patients enough time to consider their decisions?¹¹³

I0005 QUESITO: Is it possible to obtain an advance directive on the use of the technology?¹¹⁴

SOTTOCRITERIO: Individual

H0006 QUESITO: How do patients and important others react and act upon the technology?¹¹⁵

SOTTOCRITERIO: Communication

H0007 QUESITO: What is patients' and important others' knowledge and understanding of the technology?¹¹⁶

H0008 QUESITO: How is the information regarding the use of the technology processed and exchanged?¹¹⁷

¹⁰⁹ DESCRIZIONE: Is the common professional practice of discussing the treatments with patients enough, or is special care needed with this technology? The technology to be used in life-threatening situations may have life-threatening side effects (e.g. invasive technique). Technology used to get exact information may have unexpected severe side-effects (e.g. miscarriage due to amniocentesis). FONTI INFORMATIVE: Literature search. Expert opinion. Registers.

¹¹⁰ DESCRIZIONE: Technologies may change the relationship between physician and patient, challenge professional autonomy or otherwise interfere with professional ethics and values. The patient-physician relationship is traditionally based on mutual trust, confidentiality and professional autonomy so that individual treatment decisions can be made in the best interest of the patient. Technologies that interfere with core virtues and principles of medical and professional ethics challenge the professional integrity of the physicians or other health care professionals. Technologies that align with professional ethics are more likely to be implemented successfully. FONTI INFORMATIVE: Expert opinion.

¹¹¹ DESCRIZIONE: It is important to provide information on the (evermore complex) technologies in such a manner that the patient can truly understand it. FONTI INFORMATIVE: Explanatory report to Biomedicine convention.

¹¹² DESCRIZIONE: The concept of informed consent includes also the possibility to consider other therapeutic options, if these are available. FONTI INFORMATIVE: Explanatory report to Biomedicine convention.

¹¹³ DESCRIZIONE: It is usually advised that the patient is given some time to think over the treatment decision, especially if the decision involves assimilating complex technical information or a tough weighing of risks and benefits of the procedure. It should be assessed beforehand if a given technology allows such time for consideration.

¹¹⁴ DESCRIZIONE: If it is expected that the technology may be used in an emergency situation in the future it is advised that the patient is consulted beforehand and her opinion is recorded to the medical file as an advance directive on the use of a given technology.

¹¹⁵ DESCRIZIONE: This issue is about the patients and her important others' attitudes, perceptions, preferences, satisfaction and relations to the technology. This covers whether, from a patient perspective, any positive or negative QUESITO arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences (e.g. insecurity, worries, hope, anxiety, stigmatisation, person's value as a human being or social status, courage to face life, satisfaction, changes in self-conception). FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

¹¹⁶ DESCRIZIONE: This QUESITO explores the patient's and important others' understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) they need before, during and after the use of the technology. FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

¹¹⁷ DESCRIZIONE: This issue is about the exchange of information from a patient's perspective. What are patients' and significant others' questions? How do they receive answers? How is information provided and received? FONTI

All patients provide written and informed consent for the diagnosis examinations and for the procedure C (Paciaroni, et al., 2011).

H0009 QUESITO: What are the consequences in decision making?¹¹⁸

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Criterion C19 – Pressure of interest groups (citizens, professionals, industry, press)

Fonti: letteratura, opinione di esperti, ascolto degli stakeholder

Da fare: citare nel testo le fonti più importanti inserendo la citazione a piè di pagina (*in Word 2010: Riferimenti / Inserisci nota a piè di pagina*)

Domande:

- La tecnologia è in grado di modificare convinzioni religiose, morali e culturali, o credenze di alcuni gruppi, o cambiare attuali ordinamenti sociali
- Quali potrebbero essere le conseguenze nascoste della tecnologia e del suo utilizzo per gli stakeholders?
- L'uso della tecnologia può alterare la realizzazione dei diritti umani di base?

SOTTOCRITERIO: Major life areas

H0001 QUESITO: Which social areas does the use of the technology influence?¹¹⁹

H0002 QUESITO: Who are the important others that the use of the technology may affect in addition to the patient?¹²⁰

SOTTOCRITERIO: Principal questions about the ethical aspects of technology

F0003 QUESITO: What can be the hidden or are there unintended consequences of the technology and its applications for different stakeholders?¹²¹

SOTTOCRITERIO: Beneficence/nonmaleficence

F0011 QUESITO: Can the technology harm any other stakeholders? What are the potential benefits and harms for other stakeholders, what is the balance between them? Who will balance the risks and benefits in practice and how?¹²²

INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

¹¹⁸ DESCRIZIONE: This issue clarifies the possible implications from the patient's perspective to decision making e.g. limitations (dependent, passive user) and possibilities (empowered, active user) as a consequence of using the technology.

FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

¹¹⁹ DESCRIZIONE: Map the major life areas of the patient and the important others (family life, day care, school, work, leisure time, lifestyle, or other daily activities), where the technology is going to be used or where its use may have a direct or indirect influence. FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

¹²⁰ DESCRIZIONE: Describe who are the important other people that are involved in the use of technology in addition to the patients (parents, children, friends, people at work place etc). FONTI INFORMATIVE: Search for or conduct a literature review or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals and content experts can be consulted.

¹²¹ DESCRIZIONE: In addition to intended use, the technology may be used for other purposes and have side-effects in addition to those following from the intended use. Unintended consequences are obviously difficult to predict, but the intended purpose and uses of the technology should be evaluated against the likely uses and consequences of the technology in the real world. New technologies tend to lead to new areas of inventions and give rise to new ethical questions (e.g. IVF and development of genetic testing has led to questions of preimplantation genetic diagnostics (PGD). As presymptomatic and prenatal genetic tests have become available, the health care system has to be prepared to handle moral QUESTIONS raised by true positive and false negative findings.) Many treatments have indirect effects also on relatives. FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder.

¹²² DESCRIZIONE: Some technologies have the potential to unfold unwanted or harmful effects not only on the patients that the technology is directly applied to but also indirectly on other stakeholders (relatives, other patients, organisations, commercial entities, society etc.) Benefits and harms to individuals must be balanced with benefits and harms that can befall society as a whole (social utility, maximizing public health). These harmful effects may manifest in the physical, social,

SOTTOCRITERIO: Culture

G0010 QUESITO: How is the new technology accepted?¹²³

G0011 QUESITO: How will the other interest groups of the new technology be taken into account in the planning / implementation of the new technology?¹²⁴

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Criterion C20 – Historical and political context

Fonti:

Da fare: citare nel testo le fonti più importanti inserendo la citazione a piè di pagina (*in Word 2010: Riferimenti / Inserisci nota a piè di pagina*)

Da fare:

- Quali saranno le conseguenze dell'implementazione/non implementazione della tecnologia sulla giustizia del sistema sanitario?
- Sono rispettati i principi di utilità, giustizia e solidarietà?

SOTTOCRITERIO: Ownership & liability

I0019 QUESITO: Does the technology infringe some intellectual property right?¹²⁵

SOTTOCRITERIO: Legislation

F0016 QUESITO: Is legislation and regulation to use the technology fair and adequate?¹²⁶

SOTTOCRITERIO: Legal regulation of novel/experimental techniques

I0029 QUESITO: Is the voluntary participation of patients guaranteed properly?¹²⁷

financial or even other domains of life. For example results of genetic tests may negatively interfere with the family planning and social life of not only the individual being tested but also of his or her relatives. Changes in the availability of diagnostic tests may significantly alter the requirements placed on the health care system. Table 2 in the process description can be used to describe benefits and harms. FONTI INFORMATIVE: Literature search. Expert opinion. Stakeholder hearing.

¹²³ DESCRIZIONE: Acceptance should be looked at by different perspectives: by organisation, by personnel and by patients. A new technology could consist of elements which don't suit the image of the organisation. Also, the alternative ways to introduce a new technology into the organisation could influence problems e.g. resistance among staff and dysfunction of processes. Patients are usually very technologically-oriented. However, patients can resist a new technology itself or its implementation. Objective and understandable information on a new technology is important. FONTI INFORMATIVE: Systematic reviews (and other studies), qualitative research methods.

¹²⁴ DESCRIZIONE: It may be useful to know who are the possible stakeholders of the particular technology, as well as what kind of co-operation there has been and what kind of interaction is needed. The stakeholders could be e.g. the pharmaceutical industry and companies offering new technologies, authorities (national / regional), administrative parties, municipalities, policy makers / decision makers, staff groups and patient organisation. One can also ask: Has the patient organisation taken part into the process? Has it been involved from the beginning (in the planning) or in the later stages for example as commentator? Furthermore, it is interesting to figure out what kind of co-operation exists between hospitals and companies offering new technologies and what kind of co-operation is needed. FONTI INFORMATIVE: Systematic reviews (and other studies), qualitative research methods.

¹²⁵ DESCRIZIONE: QUESITO in this topic are to be considered by the health care unit when considering the acquisition of a new technology. The wording of acquisition contract may affect liability sharing between the manufacturer and health care unit. FONTI INFORMATIVE: Manufacturer, patent data bases, EPO Web site.

¹²⁶ DESCRIZIONE: Technology may lead to ethical problems that make current regulation inadequate (e.g. ethical reflection is needed when considering what kind of regulation is needed. This consideration is done on the basis and in combination with the legal domain. Emphasis should be put on considering the ethically relevant aspects and consequences of current law, needs for legal regulation that have arisen from the ethical analysis, and a global assessment of the adequacy of the legislation based on all available information. FONTI INFORMATIVE: Law, rules and regulations. Stakeholder hearing. Expert opinion.

¹²⁷ DESCRIZIONE: Use of experimental technologies may not compromise patient safety. Patients must not be pressured into such treatments.

I0026 QUESITO: Is the technology so novel that existing legislation was not designed to cover its regulation?¹²⁸

I0027 QUESITO: How the liability issues are solved according to existing legislation?¹²⁹

I0028 QUESITO: Are new legislative measures needed?¹³⁰

¹²⁸ DESCRIZIONE: Modern biomedical sciences produce novel technologies which may not always be unambiguously covered by existing provisions.

¹²⁹ DESCRIZIONE: If the current law does not provide a straightforward answer to the liability Issue it may be advisable to consult a legal expert on the interpretation of the existing provisions with regard to the technology in question. This way the health care unit can prepare itself for the possible future legal proceedings.

¹³⁰ DESCRIZIONE: If the existing legislation is not satisfactory the introduction of a novel technology may require new legislative measures. At the level of a health care unit this may slow down the introduction, whereas at the level of the society it implies a need to use resources for preparing new laws.

Dimension D8: Organizational Impact

Criterion C21 – System capacity, appropriate technology use

Fonti:

Da fare: citare nel testo le fonti più importanti inserendo la citazione a piè di pagina (*in Word 2010: Riferimenti / Inserisci nota a piè di pagina*)

Domande:

- Quali sono i benefici/rischi per il paziente, e come varia il bilancio rischio/beneficio introducendo o meno la tecnologia? Chi e come bilancerà i rischi e i benefici?
- La tecnologia può danneggiare qualche altro stakeholder? Quali sono i benefici e idanni per gli altri stakeholders? Chi e come bilancerà rischi e benefici?

SOTTOCRITERIO: Process

G0001 QUESITO: What kind of work flow and patient flow processes are needed?¹³¹

Implantation Procedure

Procedures are conducted in the cardiac catheterization laboratory conscious sedation (1.5%), local (76.4%) or general (22.1%) anesthesia. Sedation is given to relieve anxiety and enable the imaging cardiologist to perform a TEE during the procedure. A 7-Fr femoral sheath is inserted into the left femoral vein. The right femoral vein is used to insert the intracardiac echocardiography (ICE) catheter for further visualization of the septal defect. If ICE catheters are not available, a TEE is performed to provide imaging **SC** (Bissessor, et al., 2011).

However, while TEE requires sedation or general anaesthesia, and entails the risk of aspiration, ICE is costly and adds incremental risk to the procedure. Moreover, both imaging modalities considerably lengthen the procedure **SC** (Wahl, et al., 2008).

A 5-Fr sheath in the femoral artery provides intra-arterial blood pressure monitoring. All patients receive antibiotics, aspirin, and clopidogrel the day of the implantation and are heparinized during the procedure to an activated clotting time of at least 250s **SC** (Bissessor, et al., 2011). In 72.1% of patients, size and morphology of the PFO are determined using an NMT sizing balloon. The septum is usually crossed with a Cournand or multipurpose catheter on a J-tipped wire, thus it is exchanged for an Amplatz stiff wire and positioned in the left upper pulmonary vein to allow passage of the delivery sheath **SC** (Alameddine, et al., 2004).

The devices reach the defect in delivery catheters using multimodality imaging. Optimal positioning and final release are accomplished after the echocardiologist and the interventionalist (deploying the device) are in agreement. Immediate procedural success is determined by assessing the residual shunt on color Doppler and visualizing the device and the closed defect on ICE/TEE. The patient undergoes standard cardiac catheterization monitoring and nursing during the procedure. The average procedure duration is 43.5 ± 26.3 min and the average fluoroscopy duration is 10.6 ± 9.5 min **SC** (Alameddine, et al., 2004).

Postprocedure, the patient is started on aspirin and clopidogrel for a period of 3 months. Lifelong aspirin is only recommended for cryptogenic stroke by the neurologist. Patients are allowed to mobilize postsedation when hemostasis is achieved with removal of the venous sheaths. The patient is then admitted to the cardiac ward for a monitored overnight stay. On Day 1 postprocedure, a transthoracic echo is done to exclude device embolization and assessment for “coin slotting” and positioning. This is repeated at 3 months, 6 months, and 1 year. At 6 months, a TEE is done to assess the residual shunt when the shunt was deemed to be greater than mild on color Doppler after 1 month. Trivial and mild shunts postprocedure are expected to disappear with endothelialization of the device which can take up to 30 days **SC** (Bissessor, et al., 2011).

G0002 QUESITO: What kind of patient and relative involvement in treatment or care has to be mobilized?¹³²

¹³¹ DESCRIZIONE: A new technology could change current work tasks and processes (including also quality control). Work and patient processes should be described, and it should be explained what kind of activities a new technology might replace or reduce in the target organisation. Patient flow and changes required in patient path should be taken to account when implementing new technology. It is essential to know the change the use of the new technology generates to the performance of care. FONTI INFORMATIVE: Systematic reviews (and other studies), annual reports and statistics of the hospital, other qualitative research methods.

¹³² DESCRIZIONE: A new technology may require changes in the distribution of tasks among the people involved in the treatment and care. Patients and their important others may be more actively involved in own care and treatment – or tasks they used to carry out may be taken over by health professionals.

G0003 QUESITO: What kind of staff, training and other human resources is required?¹³³

Hemodinamists are needed in hemodynamic rooms: when also a cardiac surgery room is present in the hospital, usually staff is more competent and qualified in order to manage emergency and more complex situations requiring cardiac surgical intervention. On the other hand, hemodinamists working in ospitals without cardiac surgery room are more single procedure-oriented, thus they don't have competences in emergency cases **G** (Barbieri, 2012).

G0004 QUESITO: What kind of co-operation and communication of activities have to be mobilised?¹³⁴

SOTTOCRITERIO: Investments and tools required to use the technology

B0008 QUESITO: What kind of special premises are needed to use the technology?¹³⁵

The specific tools which are needed in the hemodynamic/angiographic room are (Lombardy Region, 2011):

- Digital angiography equipment
- Medical surgical aspirator
- Emergency cart
- Defibrillator
- Electro scapel
- Blood/gas analyzer
- Gas flowmeter
- Angiographic injector
- Scialytic lamp
- Laryngoscope
- Patient monitoring
- Polygraph
- Syringe pump
- Infusion pump
- Oximetry
- Sphygmomanometer
- Ultrasound probe
- System printer
- Body temperature thermoregulation
- Pulmonary ventilator
- Diagnostic imaging workstation
- labp
- Radiofrequency
- Ultrasonography
- Electrocardiograph

¹³³ DESCRIZIONE: It has to be clarified what kind of staff is needed, and whether the existing staff can be trained or extra staff must be brought in. A new technology can bring along the need for extra staff when extending the ongoing activities in the organisation or when there is a demand for special expert knowledge. It must be considered if there will be a need to increase or decrease the amount of the staff. The implementation of a new innovation can mean change in job satisfaction. It could make some tasks monotonous or bring along new boring job descriptions. It is crucial that there is not just one person familiar with the new technology. If just one person has been trained for a new technology, there is a risk of losing know-how when he/she leaves the organisation (or moves to other tasks). FONTI INFORMATIVE: Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods.

¹³⁴ DESCRIZIONE: The use of technology can presume new co-operation and communication with other parts of the structure (e.g. other units) or outside the structure (e.g. other hospitals, pharmacies). The type of technology 'determines' the frequency of need for information exchange between different actors. Also interaction and communication with patients and their important others will change. FONTI INFORMATIVE: Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods.

¹³⁵ DESCRIZIONE: Many technologies require purpose-built premises within organizations, such as radiation-secured areas, Faraday cages, etc. Typical premises in primary or secondary care may differ markedly from country to country. A clear description of necessary facilities, training etc. is needed instead of lump statement (e.g. to be used in hospitals only). FONTI INFORMATIVE: Manufacturer, applicability studies, clinical experts, user information. National or local judgement.

SOTTOCRITERIO: Management

G0008 QUESITO: What management problems and opportunities are attached to the new technology?¹³⁶

G0009 QUESITO: Who decides which patients are to undergo a treatment and on what basis?¹³⁷

SOTTOCRITERIO: Change in management

D0023 QUESITO: How does the technology modify the need for other technologies and use of resources?

SOTTOCRITERIO: Training and information needed for utilizing the technology

B0012 QUESITO: What kind of qualification, training and quality assurance are needed for the use or maintenance of the technology?¹³⁸

Adverse events' risk is inversely proportional with the operator experience, thus, according to the American recommendations, a qualified operator should have a practice of at least 10 interventions with a supervisor and implement at least a minimum of 10 interventions per year in order to maintain a proper expertise R (Balbi, et al., 2010).

B0013 QUESITO: What kind of training is needed for the personnel treating or investigating patients using this technology?¹³⁹

B0014 QUESITO: What kind of training and information are needed for the patients receiving or using this technology & their families?¹⁴⁰

B0015 QUESITO: What information do patients outside the target group and the general public need on the technology?¹⁴¹

SOTTOCRITERIO: Occupational safety

C0020 QUESITO: What kind of occupational harms may exist through using the technology?¹⁴²

SOTTOCRITERIO: Environmental safety

¹³⁶ DESCRIZIONE: The QUESITO concerns the administrative / managerial questions of the new technology: management of resources (e.g. investments), co-ordination (in relation to different levels), establishment of objectives, monitoring and control, evaluation and sanctioning.

¹³⁷ DESCRIZIONE: Procedurals about decisions about the patients who receive care could vary. FONTI INFORMATIVE: Systematic reviews (and other studies), reports of the hospital or hospital districts and other qualitative research methods.

¹³⁸ DESCRIZIONE: We need to differentiate between the users who are. 1. applying the technology (could be different from those interpreting results) 2. interpret the results and make treatment decisions. 3. take care of service and maintenance. Training materials: writing and/or translation, other adaptation? Personal training: individual and/or group sessions, number and length of sessions, number and qualifications of trainers. Are regular/ frequent standardisation or quality checks required? E.g. CME points. FONTI INFORMATIVE: Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information. National or local judgement.

¹³⁹ DESCRIZIONE: Training materials: writing and/or translation, other adaptation? Personal training: individual and/or group sessions, number and length of sessions, number and qualifications of trainers. If the technology requires a specific skill that is developed over a period of time using the technology (learning curve) it should be estimated how many cases a professional needs to treat (as a basis or per year) in order to reach acceptable quality. FONTI INFORMATIVE: Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information. National or local judgement.

¹⁴⁰ DESCRIZIONE: Training materials: writing and/or translation, other adaptation? Personal training: individual and/or group sessions, number and length of sessions, number and qualifications of trainers. FONTI INFORMATIVE: Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information, patient organisations. National or local judgement.

¹⁴¹ DESCRIZIONE: Training materials: writing and/or translation, other adaptation? Informed consent for participating? FONTI INFORMATIVE: Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information, patient organisations. National or local judgement.

¹⁴² FONTI INFORMATIVE: Research articles, manufacturers' product data sheets, safety monitoring databases.

C0040 QUESITO: What kind of environmental risks may use of the technology cause?¹⁴³

SOTTOCRITERIO: Safety risk management

C0060 QUESITO: How does the safety profile of the technology vary between different generations, versions or products?¹⁴⁴

C0061 QUESITO: Is there evidence that harms increase or decrease in different organizational settings?¹⁴⁵

C0062 QUESITO: How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?¹⁴⁶

C0063 QUESITO: How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?¹⁴⁷

C0064 QUESITO: How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)?¹⁴⁸

¹⁴³ FONTI INFORMATIVE: Research articles, manufacturers' product data sheets, safety monitoring databases.

¹⁴⁴ FONTI INFORMATIVE: Research articles, manufacturers' product data sheets, safety monitoring databases.

¹⁴⁵ FONTI INFORMATIVE: Accuracy and effectiveness research, epidemiological risk research.

¹⁴⁶ FONTI INFORMATIVE: Is there a requirement for specific training, use of a protocol or guideline or restricting use to specialist centres, providing patient information, etc. may all reduce the occurrence or severity of harm.

¹⁴⁷ FONTI INFORMATIVE: Research in occupational health and safety.

¹⁴⁸ FONTI INFORMATIVE: Research articles, manufacturers' product data sheets.

6. Discussion

The implementation of the VTS-HTA approach, as described in the previous chapters, is complex and has both strengths and drawbacks to be taken into account. On the one hand, the standardization and explicit regulation of the HTA process can instill uniformity and transparency in a process that may be highly elusive. While subjectivity cannot be completely removed – as the notion of “implicit criteria” also suggest - the framework seeks to minimize discretion in decision making and achieve decisions that are perceived as legitimate by the stakeholders. Key elements of the framework – e.g. the adoption of models such as EUnetHTA elements and EVIDEM criteria; the commitment to Evidence Based Medicine in the form of systematic reviews and the reliance on field experts – all manifest an intention to legitimize decision making as rigorous. On the other hand, the VTS framework is a complex engine whose standards and requirements may ensue rigor and legitimization at the expense of flexibility, adaptability and timeliness.

The opportunity to standardize and formalize the framework, indeed, can be better understood with the intention to “push” the practice of HTA into a community of stakeholders that was unused to HTA (Radaelli, et al., Working paper). As a matter of fact, its actual implementation is still “in fieri”, since only results of savings with desk-rejected technologies are available, while the ongoing evaluations are facing criticalities that prevented the achievement of full completion and the definition of a proper protocol.

There are many issues that still could be changed, as clear evidence from literature lacks and different international organizations haven’t shown yet a well-defined way of selecting and involving decision makers, or taking advantage of a structured decision model for priority setting in healthcare. Furthermore, Multi-Criteria Decision Analysis is only one of the methods available to structure and present information for decision making, and HTA evaluators should be ready to field test how tools, learned from more organized groups, can actually be employed on their specific context, according to different needs, decision makers’ features and principles, and normative and political background. Limitations on resources, time and information make the decision process even more complex, thus a robust and properly balanced model is necessary when assessing the value of health interventions and their related outcomes on diseases’ prevention and patients’ life. When designing the framework, both pragmatic and reasonable rules have to be taken into account, while considering not only effectiveness, but also costs and organizational impacts of technologies under evaluation.

These main remarks moved the argumentations which will be undertaken throughout the next paragraph. A factual contribution to the observed process was thought to be the formulation of

recommendations which could be useful to improve the current practice, while helping a critical reflection on assets and drawbacks of the procedure itself.

6.1 Recommendations and Impacts for Lombardy Region

In this chapter, the main issues which emerged from the analysis of the current “as-is” process in Lombardy Region will be exposed in-depth with the proposal of “should-be” options for change, then the recommended solution will be discussed, by adding implications for the system itself as well. More specifically, while investigating the three main steps of the VTS framework, i.e. Prioritization, Assessment and Appraisal, some questions arose regarding the two latter phases, thus requiring a further testing of usability of documentation and tools which are available to the VTS actors, as well as an investigation of the proper organizational structure to consistently achieve the goals of each step.

As summarized in the table below, issues are mainly connected to two streams, the MCDA components’ and the organizational structure’s ones: advices are provided in the right side, thus being distinguished in major “R” or minor “r” recommendations, according to their level of urgency.

AS-IS	SHOULD-BE
MCDA issues	
<i>1. Scores – The twofold question regards the current low level of engagement of TTRAM members: is low participation due to the complexity of the process itself, to the necessity of creating an alignment of competences into the group, and to the lack of appropriate information? Why should they express different scores for a certain evaluation, instead of a univocal performance level?</i>	R1. Scores, which represent the performance of the technology under evaluation related to the different criteria, should be first suggested by Assessment experts themselves, who express a “univocal utility function” that is directly connected to both their literature review and their knowhow, in order to provide a first orientation for TTRAM members and further engage them in a better understanding of the SIM.
<i>2. The first two criteria, i.e. C1 – Completeness and consistency of documentation and C2 – Relevance and validity of documentation, are considered additive to other ones, while already affecting their evaluation. Is it right that evaluations with a higher grading of C1 and C2, but poorer in other criteria, have more advantages than those ones where happens the opposite?</i>	R2. C1 and C2 should be separated from other criteria, since their evaluation is already implied when rating other criteria themselves;
<i>3. Why issues are repeated in some SIM criteria, thus creating overlapping information?</i>	r3. Overlapping issues should be eliminated in order to make the asking and answering process leaner and more understandable with mutually exclusive information.
<i>4. Weights – Why the weighting scale has limited 1-15 ranking, being adapted in order to avoid the association of the same mean weights?</i>	r4. The weights could be freely associated to criteria with the allocation of 100 points.
<i>5. Why weights of distinct groups of technologies should be maintained different?</i>	R5. Weights should be maintained different in order to avoid bias which may occur if the specific context is not thoroughly taken into account.

Organizational Structure issues	
1. Does an Assessment group composed of only clinical experts have the most appropriate capacities to provide an overall documentation about the technology of interest, to indicate possible lacks on methodologies, or to specify how to edit a HTA report?	R1. The panel of experts should include not only clinicians or health staff, but also properly selected patients' associations, health economists, and personnel with organizational competences, in order to take part to the elicitation of literature and to more effectively complete the SIM issues.
2. Does the TTRAM composition affect the usefulness of the MCDA Index? Should a proper balance of covered areas be reached in order to guarantee more reliability of results?	R2. The TTRAM group should be well-balanced according to different areas and understanding of the process, while the MCDA Index should be taken into account as a means of legitimizing appropriateness of use judgment.
3. Is the VTS-HTA program sustainable over large scale evolution of the activity?	R3. The VTS program will have to clearly define in which situations is needed to develop a HTA report (HTA Doers), and when to endorse already available studies properly checked and validated (HTA Users). In order to make the process of technology evaluation faster, a structured protocol for the Assessment phase has to be detailed from the perspective of a future increase of requests.

Table 6.1 - AS-IS current problems and related SHOULD-BE proposals

6.1.1 Multi-Criteria Decision Analysis Issues

1. Scores – The twofold question regards the current low level of engagement of TTRAM members: is low participation due to the complexity of the process itself, to the necessity of creating an alignment of competences into the group, and to the lack of appropriate information? Why should they express different scores for a certain evaluation, instead of a univocal performance level?

Recent analyses of the involvement of TTRAM members to the Appraisal activities report that almost half of the group participates to less than 1/3 of meetings, as shown in the figure below, while contributions of weighting and scoring are almost null (Arioli, 2012).

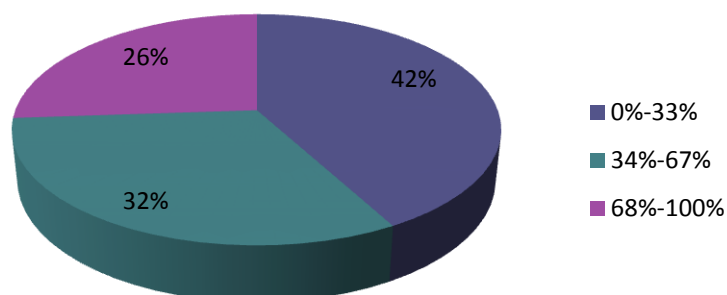


Figure 6.1 - Percentage of TTRAM participation to the VTS-HTA process

Reasons for this phenomenon are not clear yet, however answers to a questionnaire provided focus points that referred to the complexity of the internet portal and its web forms, to the lack of a methodological guide, and to the necessity of more practicality during meetings, in order to create involvement to solve possible doubts. More specifically, an example of responses about upsides, but most of all downsides (i.e. the easiness of consultation), of the internet portal is provided in the chart below, highlighting the necessity of improving this criticality.

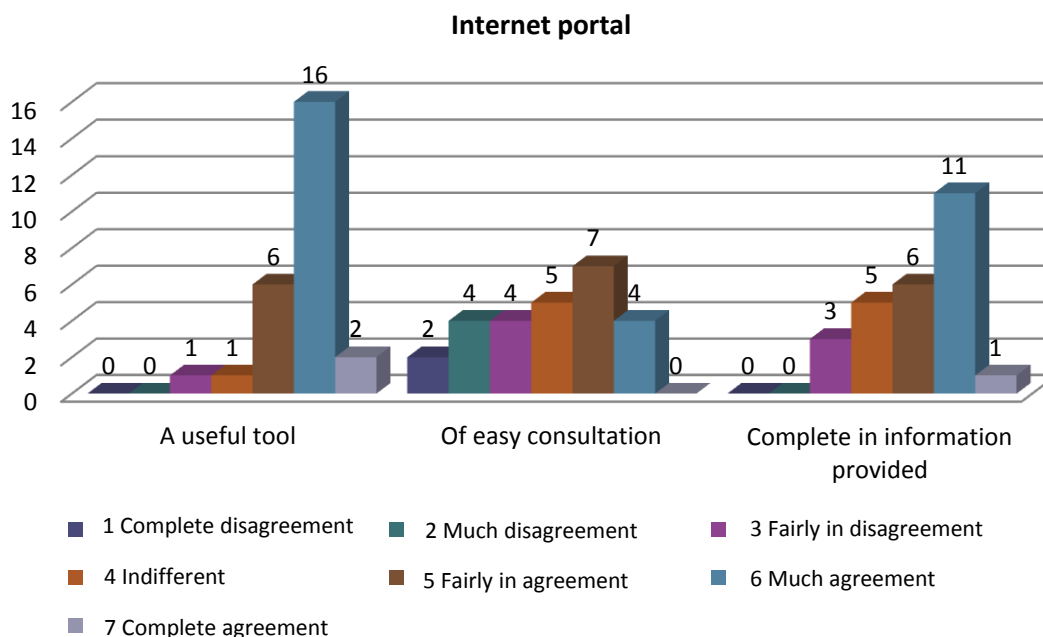


Figure 6.2 - Frequencies of TTRAM answers (on a total of 26 respondents) regarding the internet portal

The problem of the TTRAM engagement is thus connected to the need for a full understanding of how the process works, how tools have to be properly used, and what is the sufficient information to be shared among components, from which depend the achievement of an effective final result. If a more robust training of participants and an alignment between the different competences are not provided, a pertinent codification of the documentation which is output of the previous Assessment phase is uncertain, preventing in this way the untroubled continuity of the overall process to its end. Furthermore, the attainment of the same starting level of knowledge on the topic of interest, from the Appraisal group's perspective, is related to how the SIM conveys information emerged and collected from both the systematic literature review and the knowhow of Assessment experts. In fact, only when documentation is clear and useful, it can be more easily translated in judgments by the Appraisal – non-expert – members. Even though an external and not biased group has to express a rational and reasonable final judgment, sometimes thorough awareness and understanding of specific efficacy and effectiveness results, or safety data, for instance, are not possible due to legitimate inexperience about topics related to the healthcare technology under evaluation.

A second related question is: “Why scores of a certain evaluation, expressed by a jury, should be different?”; since ratings specify how the technology of interest performs according to the different criteria, a variation between them shouldn’t be present. Indeed, different decision makers would provide different ratings when their codification of information is mistaken, or, most importantly, when they associate dissimilar importance not to criteria, but to issues included in criteria themselves. This can be defined a bias, as it can only occur in case of lack of proper thresholds or a well-balanced and certain overview on the actual state. That’s why usually in most practices a score average is calculated or the group reaches a consensus on a “univocal utility function” which expresses the overall performances stratified by criteria. Thus, in the VTS form the 0-3 discrete scale, besides the 0 score, is unambiguous, but a straight judgment isn’t possible for those who are not into the topic and the SIM itself can result too specific and of difficult interpretation for them.

The rationale for scores on the VTS online forms represents, in fact, a first minor sub-issue, as, for instance, in the discrete 0-3 scale the value 0 not only stands for lack of information, but also for the lowest performance of the technology, which implies that no difference is expressed by two basically different statements into the overall MCDA Index and its related final judgment support. Moreover, the second sub-issue is that thresholds for proper assessment of indicators, for instance mortality, morbidity or average complication rates of a certain intervention, are not provided by the Assessment Workgroup, thus non-experts’ interpretation of end-results could be further misapplied to the decision making tool.

A new approach, which could enable the VTS process to both strengthen the participation of the Appraisal members and solve possible biases incurring in their SIM codification, should be the suggestion of scores directly by the panel of experts, who have already undertaken the systematic literature review and could provide further comments and explanations which corroborate their anticipatory evaluation, according to their specific knowhow. In fact, on the one hand, the TTRAM group could have well-explained reference points to which compare personal opinions from the SIM elicitation, thus increasing their participation to the process, while, on the other hand, scores are univocally proposed as a factual and reliable clarification of the technology performance related to criteria. Moreover, as scores are based on available quantitative and qualitative evidence and technical judgments (where necessary) from the panel, not only should each panel member have a clear understanding of dimensions, but it is also crucial that members have the same, shared, understanding (Peacock, et al., 1997). Thus, the achievement of consensus on a certain topic is indeed important to improve accountability, credibility and acceptability of results (Baltussen, et al., 2010). For instance, in consensus conferences multidisciplinary experts themselves identify indicators

and proper recommendations, however comments explaining scores have to be clear and not ambiguous (SNLG, 2009).

This proposal is grounded on some starting Canadian experiences, where MCDA evaluations were implemented in order to set priorities in healthcare interventions: in the first example, the EVIDEM Collaboration provided applications of the MCDA framework, where, after the redaction of a HTA report, specific panelists were involved in the process of weighting and scoring criteria; on the one hand, in the evaluation of growth hormone for Turner syndrome, the panel was designed to include relevant stakeholders, with a focus on experts in the disease to explore relationships between policy and clinical decision making (Goetghebeur, et al., 2010). On the other hand, in a recent study for medicines evaluation, the appraisal group specialists were nonrandomly assigned the medicines associated with their specialty, then randomly assigned to other medicines (Goetghebeur, et al., 2012). In both cases, a scoring scale of 0 to 3 with defined anchors and scoring examples was provided; moreover, the MCDA Value Matrix included features to collect feedback on the synthesized data and the evaluating process, and to specify whether a low score was due to data limitation. Furthermore, a CADTH experience regarded the optimization of health system use of medical isotopes and other imaging modalities, where the evaluation group was a purpose-built, project-specific committee which was recruited in order to specifically leverage the experience of these individuals and also to ensure that duplication of effort was avoided. After the literature search, which was performed by an information specialist using a peer-reviewed search strategy, the scoring activity was differentiated: those criteria related to the underlying condition were permitted only positive values (range: 0 to +3), while criteria comparing a imaging modality with alternative ones had negative or positive values (range: -3 to +3). A rating of 0 was interpreted to mean that, for that particular criterion, there was no difference between the alternative test and the imaging test of interest. Finally, validation was achieved through consensus, while the process was not intended to be used as a “calculator”; rather, the intent was to collect and organize information and summarize it in a consistent manner (Mujoomdar, et al., 2012).

These two examples are important to show how MCDA could provide a robust group decision support system, as the process of scoring supports the participants’ deliberative process by promoting systematic consideration of a wide range of decision criteria and by making the appraisal process and the reasoning behind it more explicit. It may be considered valuable to force people to think through each concept when evaluating a new healthcare intervention, furthermore this process would highlight those facets of the data about which an appraisal committee may have concerns (Goetghebeur, et al., 2012). Thus, from an MCDA perspective, the two main roles are the expert role,

who determines impact scores based on scientific evidence, and the decision maker role, who weights criteria according to political preferences, prioritizing options.

In the VTS framework, the two roles are entwined into the figure of the final jury, however whether to keep them separated or not still represents a dilemma: in fact, to enhance the quality of the 'objective' analysis, the most knowledgeable persons should be involved in the construction of the impact documentation and performance judgments; this usually means that the two functions are separated. On the other hand, to secure commitment from the most influential actors in the policy arena, these persons must agree wholeheartedly with the procedure, thus this calls for more 'braiding' between the two roles (Bots, et al., 2000). Hence, as showed by the previous cases, evidence from practice clarifies that, when dealing with this typology of decision making tool, the legitimization of a choice has to be first validated by direct expert authority. As a matter of fact, specialist who conduct and collect both literature search and their own personal knowledge about a certain intervention, while introducing a first conception of things, could be also responsible for suggesting and providing proper reasons for scores. Practically, this would mean that, after a thorough literature review and the collection of information into issues of the SIM, experts, who have been already divided in groups to better focus on some dimensions, simply indicate at the beginning of each criteria a recommended grade for the following activity of scoring performed by the TTRAM members. This operation, as previously mentioned, would be twofold: on the one hand, it will enable experts to provide a more effective and usable SIM to the appraisal group, while on the other hand, the TTRAM will still have the right to point out its own opinion by accepting or disapproving suggestions with proper explanations. Moreover, the necessity of the final approval by TTRAM members has the purpose of validating, each component for his/her area, anticipatory judgments provided by Assessment experts, in order to confirm them with appropriate explanations or, otherwise, underline possible biases which incurred in their evaluation: in fact, thanks to its multidisciplinary settlement, many different points of view can strengthen the reliability of the decision itself.

However, healthcare decision analyses often seem to be driven by physicians' expertise and their sided opinion, which might be appropriate in the clinical setting, but which might not be appropriate in a multi-objective, multi-stakeholder context (Baltussen, et al., 2006). A possible issue in this phase is represented by the necessity of conciliating authoritativeness and tendency to "self-reference" of experts in highly specific areas by adopting a transparent and rigorous method; nevertheless, due to cost and time constraints, creating a ad hoc group, which could guarantee full balance, is not always

possible. Use of preliminary assessment exercises could facilitate panelists to become more comfortable with the MCDA method and provide appropriate representation of complex decisions.

Furthermore, in order to provide answers to the two score-related sub-issues, a minor recommendation to provide the General Healthcare Directorate with regards a deep rethinking of score descriptions, which may be sometimes misleading for evaluators. Also the lack of anchors and feedback have to be compensated, as the former prevent well-balanced judgments when Appraisal members interpret the Assessment output, while the latter precludes anonymous communication between the two groups.

For the VTS framework of Lombardy Region, the consequences of this typology of change could be nothing else but positive, as experts provide a double contribution to the Appraisal judgment, thanks to the SIM and the suggested scores, while accelerating the decision making process. First of all, the experts' panel should receive significant education and training in the principles of priority setting and decision analysis, so that ownership of the process and a meaningful and well considered discussion could be achieved by understanding the aims and techniques to be used (Peacock, et al., 1997). Thus, specialists assume the role of facilitators in order to create a link between evidence and MCDA model. Second, the TTRAM members will also have to be trained and methodologically guided to align their understanding and to create a sense of belonging to the process itself, which is mediated by an increased adequate communication among participants. The expert and stakeholder roles are to be better "braided" in order to enhance the credibility and legitimacy of the overall process, so that an initial organizational memory could be effectively created.

R1. Scores, which represent the performance of the technology under evaluation related to the different criteria, should be first suggested by Assessment experts themselves, who express a "univocal utility function" that is directly connected to both their literature review and their knowhow, in order to provide a first orientation for TTRAM members and further engage them in a better understanding of the SIM.

2. The first two criteria, i.e. C1 – Completeness and consistency of documentation and C2 – Relevance and validity of documentation, are considered additive to other ones, while already affecting their evaluation. Is it right that evaluations with a higher grading of C1 and C2, but poorer in other criteria, have more advantages than those ones where happens the opposite?

The definition of criteria C1 and C2 is briefly provided in the following table, in order to better focus on the specific concepts related to the issue:

C1 – Completeness and consistency of documentation	Measures the level of completeness (for instance, adherence to scientific standards) and consistency among different cited sources. A technology with complete and consistent scientific documentation deserves a higher grade than a technology with incomplete or inconsistent documentation. The quality of analyses provides a contribution to the value of the technology, as much as a poor analysis will limit the data comprehension, thus lowering the value of the technology itself. The grading of quality requires a critical analysis according to different international standards.
C2 – Relevance and validity of documentation	Measures the evidence of relevance of the technology for the SSR (in terms of population, disease stage, alternative technologies, outcomes, etc.) and validity according to scientific standards (e.g. study design, etc.) and conclusions (agreement between results of different studies). This includes also uncertainty considerations (e.g. conflicting results among different studies, limited number of studies and patients). An intervention with higher relevance and validity compared to international standards deserves a higher grade than a technology with lower ones. Furthermore, these affect the confidence on the technology capacity of improving health in a certain context (social, regulatory, clinical, economic), for which a critical analysis is needed.

Table 6.2 - Definitions of C1 and C2 criteria

The current method implemented in the VTS framework to assess the whole documentation found with the literature search is divided in two steps, as already mentioned in chapter 4:

- First, primary (e.g. clinical studies) and secondary documentation (e.g. literature reviews, guidelines and HTA reports) are **classified** according to tables TWE and RWE, which are associated to Evidence Based Medicine criteria and Lombardy locally adopted criteria, respectively, by giving a 1-5 point; furthermore, only level 1 and 2 are selected by Coordinators of the evaluation as the most significant studies to bring to the following step;
- Second, the **quality evaluation** of studies is different for primary or secondary sources: the former ones are separated in epidemiological, clinical, economic and budget impact documentations, then many questions assessing both consistency and relevance are to be answered, providing an overall 1-4 grade (where the grade 4 here means that the study is highly convincing and relevant); on the other hand, the latter ones are evaluated with the GET5 tool, which was created by the Health Protection Scotland, then adapted into the VTS program, and includes some yes/no questions that clearly define the acceptability of the study. This method has been considered simpler than the AGREE, however the use of this latter one, which is more robust and comprehensive, could be taken into account for future process updating.

At this point, the SIM Evidence Base is completed, moreover summarizing tables and comments, with specific additional conclusions, are provided by Coordinators of the evaluation to complete the criteria C1 and C2 of the SIM Criteria themselves. Thus, the problem is that these two features are counted twice in the overall Assessment, creating a secure ground for the MCDA Index, according to the related weight that they will deserve for each juror.

For instance, given the additive count of the first two criteria to other ones, in the MCDA result of the AS-IS procedure does not emerge that a technology with high levels of completeness and relevance of documentations, which however certify a low improvement of safety and tolerability, will have a lower index compared to another technology with less composite documentation, but which reports a higher level of safety, as the C1 and C2 criteria will always raise the basis of the evaluation. Moreover, examples such as this one clearly illustrate that there are different roles of criteria, which have to be distinguished between those qualifying evidence and those ones quantifying available information.

Thus, a new approach to this issue consists in the separation of results of the evaluation and grading of the literature level of evidence, which constitutes a knowledge base for the technology under assessment, from each rate that will be associated to the other 19 remaining criteria: in fact, the judgment of studies cannot be considered at the same level of other criteria scores, which classify actual stratified performances of the technology, since, on the one hand, they would account for different typologies of information, while, on the other hand, the representation of the final MCDA Index itself, which height depends on the multiplication of scores and weights (see figure 4.5), would provide a misleading result without a real added value for the decision of appropriateness.

As a term of comparison, the EVIDEM Quality Matrix, from which the VTS approach has been drawn, grades most relevant studies according to the three criteria describing the level of evidence, i.e. Q1 – Adherence to requirements of the decision making body, Q2 – Completeness and consistency of reporting evidence, and Q3 – Relevance and validity of evidence, thanks to instructions derived from current tools (e.g. GRADE): for each study, or group of studies, comments to specific questions, a score and the rationale for that score are provided by experts, in order to perform an ad hoc critical analysis and reach consensus. Afterwards, the whole contributions are integrated in the Quality Matrix itself, and aggregated quality scores are determined on a 0-3 scale. Finally, these three criteria performances will be endorsed in the MCDA Value Matrix (Goetghebeur, et al., 2008). Unlike the VTS, in this case the documentation is not subjected to an anticipatory classification, which could be necessary for a first skimming of relevant studies. On the other hand, it has been previously shown that NICE has adopted the GRADE methodology to evaluate the quality of evidence of studies

systematically reviewed, but the strength of recommendations, on the contrary, is assessed using standard checklists to give a rating (++, +, -) that reflect both the degree of confidence and the level of potential bias in the study findings. Furthermore, a different quantification of the effect of compared technologies is applied to economic evaluations. Thus, the evaluation methodology seems to be much direct and straightforward, even though the process itself doesn't have to be arranged to fit a mathematical model algorithm. These examples are provided in order to better focus on the importance of separating the processes of the evaluation of evidence and the scoring of performance criteria related to the technology of interest: otherwise, the term of comparison for technologies, i.e. the MCDA Index, would result unreliable and affecting in a wrong way the final judgment provided by the TTRAM members.

Moreover, this point in question links to the previous issue, as the necessity of an appropriate definition of criteria scores is here more strengthened; in fact, in the proposed approach, experts will have to provide first an external evaluation of studies, and then suggested scores with additional comments which explain how and why literature and their personal knowledge recommend a certain level of performance. Thus, statements will have to be coherently correlated to scores, in order to better provide information for the final evaluation. At the same time, as a minor recommendation, the process of Evidence Base examination and grading could be accelerated thanks to a different approach which is suggested by the National Program for Guidelines (in Italian, Programma Nazionale per le Linee Guida – PNLG), which clearly qualifies recommendations produced after a thorough systematic review on studies regarding the technology of interest, according to the indicators “level of evidence” (LE) and “strength of recommendations” (SR), which could be straight associated to VTS criteria C1 and C2. On the one hand, the LE is referred to the probability that a certain amount of knowledge is derived from studies conducted in order to produce information valid and without systematic errors, while on the other hand, the SR is referred to the probability that the application in practice of a certain recommendation leads to an improvement in the state of health of the target population. The two indicators are intertwined, however they have to be evaluated separately in order to provide the highest transparency, as in the VTS framework.

Thus, the system proposed is referred to the Center for the Evaluation of Healthcare Assistance Effectiveness (in Italian, Centro per la Valutazione dell'Efficacia dell'Assistenza Sanitaria – CeVEAS) of the city of Modena, of which the main feature consists in grounding the SR not only on the typology of study design, but also on other factors, such as feasibility, acceptability and economy of the intervention itself. The classification of a certain recommendation according to grades A, B, C, D, E doesn't reflect only the methodological quality of available evidence. For instance, there may be

cases where, even though the LE is I, the recommendation will be of type B or C, should a real uncertainty on feasibility and impact of the procedure is present.

The overall framework is thus presented below:

Level of Evidence	
Typology of Evidence	
I	Evidence obtained from many randomized controlled trials and/or systematic reviews of randomized trials.
II	Evidence from only one randomized study properly designed.
III	Evidence from non-randomized cohort studies with concurrent or historical controls or their meta-analyses.
IV	Evidence from retrospective case-control studies or their meta-analyses.
V	Evidence from case series studies without control group.
VI	Evidence based on the opinion of qualified experts or expert committees as indicated in the guidelines, or consensus conferences, or based on the opinions of the members of the working group in charge of the current guidelines.
Strength of Recommendations	
A	The execution of the specified procedure or diagnostic test is strongly recommended. It indicates a particular recommendation which is supported by scientific evidence of good quality, although not necessarily of type I or II.
B	There are some doubts about the fact that this particular procedure or intervention should always be recommended, but it is believed that its execution should be carefully considered.
C	There is substantial uncertainty in favor of or against the recommendation of performing the procedure or the intervention.
D	The execution of the procedure is not recommended.
E	It is strongly advised against the execution of the procedure.

Table 6.3 - The CeVEAS grading system

The adoption of this solution into the VTS framework is suggested in order to forward the process of grading C1 and C2, without double counting them into the other criteria's evaluation.

Consequences for the Lombardy Region system consist in the necessity of overcoming hurdles, incurring with the use of different methods, which are related to cultural and behavioral habits; however, structural and organizational changes are the first steps for process improvement. The relevance of the first two criteria on the overall Evidence Base is straight, as they provide a comprehensive analysis of available documentation and assume a predominant role, however they have to be strictly separated from other ones to prevent an unbalanced final MCDA Index result. Notwithstanding the need for formal approval from international methods, it's important to reach a balance with proper effective contextualization of procedures.

R2. C1 and C2 should be separated from other criteria, since their evaluation is already implied when rating other criteria themselves.

3. Why issues are repeated in some SIM criteria, thus creating overlapping information?

Most of SIM Criteria include overlapping issues, as they were directly incorporated and adapted from the EUnetHTA Core Model: furthermore, as shown by responses to a survey questionnaire, TTRAM members considered the SIM itself useful, complete, but also redundant (mean value 4,22 and standard deviation 1,68 on a 1-7 scale), as depicted in the charts below (Arioli, 2012):

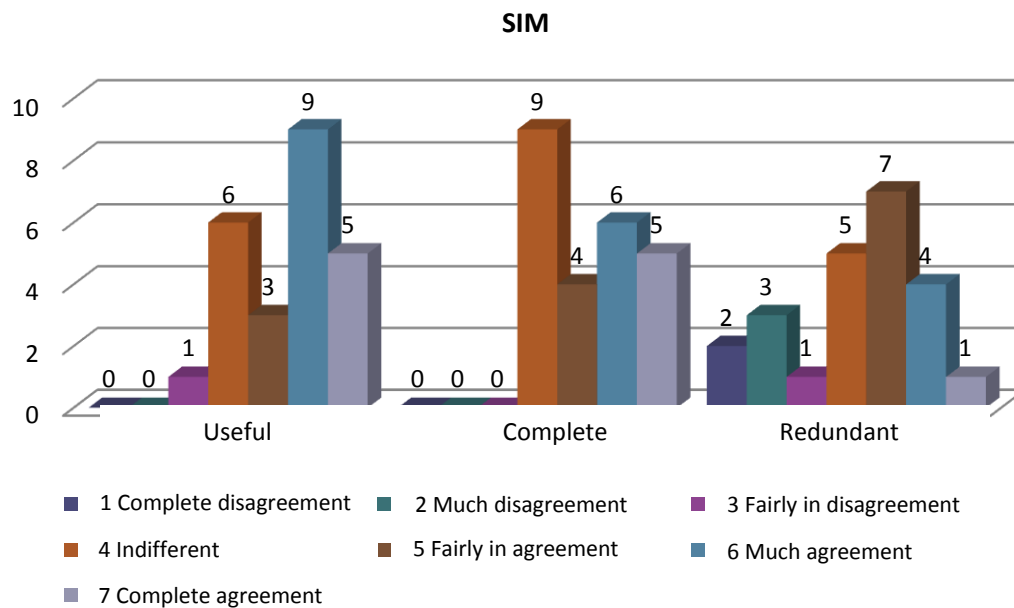


Figure 6.3 - Frequencies of TTRAM answers (on a total of 24 respondents) regarding the SIM

Coherently with the principle of providing the most rational and clear explanation of scores and related comments shown by experts, included questions should be not only exhaustive, but also mutually exclusive, in order to avoid here double counting of the same argumentations and to ensure that all relevant aspects of the experts' perspectives are captured (Peacock, et al., 2007). The Multi-Criteria Decision Analysis model that will be subsequently used to provide a final index is only a means supporting the appropriateness of use decision, as it will be later explained, however the completion of the SIM does have to be as much as possible clear and consistent, as each criterion's issue is evaluated separately, without repetitions from other ones.

r3. Overlapping issues should be eliminated in order to make the asking and answering process leaner and more understandable with both exhaustive and mutually exclusive information.

4. Weights – Why the weighting scale has limited 1-15 ranking, being adapted in order to avoid the association of the same mean weights?

Even though this represents a minor issue, in the VTS process weights are forced to be associated on a 1-15 scale, where the highest value stands for the most important criterion, paying attention to not assigning the same weight to two different criteria; weights don't sum up 100, as they will be normalized afterwards. At first, this was thought as a way to avoid that decision makers could associate the same average weights to criteria, while differentiating from the EVIDEM framework, where a 1-5 scale is used for each criterion, with subsequent normalization as well.

The activity of weighting is aimed at capturing the value system of each evaluator independent of the healthcare intervention under scrutiny: in fact, unlike the scoring procedure, the assignment of weights for each criterion reflects the relative importance to each single decision maker according to his/her intrinsic rational preferences; furthermore, they should be necessarily different, as personal value systems of stakeholders might differ depending on type of patient and type of disease. Indeed, the weighting exercise represents a means to stimulate reflection in a concrete manner and to explore actual values of committee members, highlighting the importance of the composition of decision making committees (Goetghebeur, et al., 2012).

The different approach which is suggested here refers to the free allocation of 100 points, performed by the Appraisal TTRAM members, upon previous specification of how weights have to be distributed and to which goals the process is aimed at by the General Healthcare Directorate. The proposal is grounded and inspired from the CADTH example previously mentioned: a different ranking method was performed, as experts began the weighting process first by clustering the criteria into high, medium, and low relative importance, with three to four criteria in the high and low clusters. The Medical Isotopes and Imaging Modalities Advisory Committee used a simple approach that involved the allocation of 100 points to the 11 criteria. As a starting point, each cluster was given a total weight range – high relative importance (40 to 60 points), medium relative importance (20 to 40 points), and low relative importance (10 to 20 points). Once the criteria were mapped to the appropriate level of relative importance, members were asked to rank the criteria within each cluster. Using the rankings from each cluster, final weights were assigned (Mujoomdar, et al., 2012). Furthermore, the flexible allocation of 100 points over the 15 computable criteria is recommended in Multi-Criteria Decision Analysis literature, meaning a direct expression of trade-offs between criteria according to the importance that each decision maker associates to his/her preferences (Wilson, et al., 2006): in fact, judgments which sum up 100 will be more easily applied to the algorithm itself, and the juror will learn by having a close interaction with the VTS framework. Weights can't be automatically determined as they are strongly affected by subjectivity, however the typical production of flatter preference distributions, which may lead to systematic underestimation of

tradeoffs, should be avoided thanks to appropriate understanding of the overall process (Colorni, et al., 2002).

Thus, the process of rank ordering and weighting the criteria for alternative technologies should improve the soundness of the decision making process by assessing the decision makers' preferences about the pros and cons of the alternatives and the relative priorities of the decision criteria. This step should also improve communication among decision makers about important aspects of the choice being made. On the other hand, the expression of weights is subject to political gaming as participants seek to drive the process to personally preferred outcomes (Cunningham, et al., 2009), highlighting the need for a well-balanced infrastructure. Regarding the VTS current practice, this means that the process of weighting criteria has to be as much meditated as possible, since decision makers should manifest a definite personal position, rather than avoiding to express themselves.

r4. The weights could be freely associated to criteria with the allocation of 100 points.

5. Why weights of distinct groups of technologies should be maintained different?

After the overall view on the necessity of consistency of all the components of the MCDA model, the further problem regards whether keeping weights different in comparisons not only intra-, but also inter- groups of technologies: in fact, in the former case it has been previously described that weights should be different in order to witness various points of view of different decision makers; however, in the latter one, the question of maintaining them different is still controversial, as decision makers may incur in the custom of expressing the same preferences order for all the technologies under evaluation.

In the VTS framework, a definite statement of why weights should be assigned at each evaluation hasn't been provided, however the final goal of achieving the MCDA result as a term of comparison for cost-opportunity estimate of each group of technology has always to be taken into account throughout the whole process. Specifically, the rationale standing behind the reason of different weights refers to their high dependence on the object under evaluation, as distinct considerations are to be made when dealing with specific devices or drugs, for instance, which could have a certain effect on the context: evaluating technologies with different economic impacts could, in fact, move a different ranking compared to a group of similar drugs, for which the aim is finding the best one in terms of overall health improvement. Furthermore, the organizational impact could count more in case of technology evaluations, rather than with drugs, or even the burden of a rare disease could be considered less important compared to more common illnesses. Some initial examples applying the EVIDEM framework show that, when comparing 10 different medicines covering 6 different

therapeutic areas, participants associated more importance on criteria such as “Improvement of efficacy/effectiveness”, “Improvement of safety & tolerability”, and “Public health interest” (Goetghebeur, et al., 2012), while when field testing the framework for decision making on a cervical cancer screening test in South Africa, the greatest weights were assigned to the criteria “Budget impact on health plan”, “Cost-effectiveness of intervention”, followed by “Improvement of efficacy/effectiveness” (Miot, et al., 2012). Conversely, when estimating the MCDA value of Growth Hormone for Turner Syndrome in Canada, the highly important components identified were again “Improvement of efficacy/effectiveness”, “Improvement of patient reported outcomes”, “Public health interest” and “Cost-effectiveness of intervention”, while the least important were consistently “Size of population” and “Clinical guidelines” (Goetghebeur, et al., 2010).

Changes in ranking criteria are evident and mandatory as specific objectives and critical aspects characterize different technologies under evaluation, thus the possible allocation of anticipatory weights which remain fixed for all the evaluations would cause biases due to superficial and unspecified consideration of the problem itself. In order to avoid this drawback, a different approach should be implemented, since it’s important that TTRAM members are properly trained to reflect on decisions they are responsible for and to make the decision making tool more effective and useful.

R5. Weights should be maintained different in order to avoid bias which may occur if the specific context is not thoroughly taken into account.

6.1.2 Organizational Structure Issues

1. Does an Assessment group composed of only clinical experts have the most appropriate capacities to provide an overall documentation about the technology of interest, to indicate possible lacks on methodologies, or to specify how to edit a HTA report?

The current VTS Assessment phase is characterized by the participation of a specific group of domain experts, who basically come from the clinical background and will undertake the systematic literature review in order to complete the multi-criteria assessment report, i.e. the SIM, to be provided to the next Appraisal step. However, the question is related to whether or not the best interpretation of the problem of interest is determined when only clinical professionals pass their judgments. Furthermore, in the AS-IS process, they have the responsibility of indicating possible lacks or misalignments of the used methodology and the full competences to edit the whole final document.

However, in doing so the only clinical perspective limits a broader overview on the technology of interest, not just in how the documentation is provided, but also in how it could be understood and then written down while completing the SIM issues. In years, the awareness that clinical decisions

are affected by external factors, such as economic, social, organizational and academic, took shape; indeed, specialists have only a partial control on the potential changes in clinical practice, so that additional measures, which can also work on the organization, are necessary to develop effective improvement programs (CeVEAS, 2005). Thus, the inclusion of a multidisciplinary view of a certain problem or evaluation guarantees reliability of research, as not only experts present the clinical side, but also pay more attention to the economic, organizational and socio-political contexts, thus attenuating difficulties for the following multi-criteria approach (Banville, 1998).

To better focus on the necessity of a multidisciplinary view, a further proposal is provided, as the previous reasons move towards a different approach to the redaction of the structured multi-criteria assessment report by key panelists; the process doesn't have to only consist in a simple readjustment of epidemiological, clinical and effectiveness information, but also has to give an explicit and unbiased overview which both is connected to theory and can be translated into a feasible and context-related final decision. This means that a multi-competences perspective of the Assessment phase is thus translated into a multidisciplinary composition of the Workgroup of experts, in order to offset current limitations in both literature and practice: in fact, as most of HTA reports determine clinical features and, sometimes, economical evaluations, only rare examples report the consideration of patients' needs or organizational issues in HTA processes themselves. Furthermore, this could directly cause limitations and narrow views in how both information is collected and HTA reports are published. This solution is also essential in a goal-orientated approach, as the final outcome of the Assessment phase, the SIM, has to be as much as possible exhaustive for the following Appraisal step. One of the problems emerged while writing the SIM, but also a real issue for experts of previous evaluations in the Lombardy Region process, has been the impossibility of providing answers to all the questions only through the literature review of scientific and domain papers, thus resulting in knowledge gaps brought to the final decision of the TTRAM, which could reach biased or incomplete conclusions.

The multidisciplinary basis which characterizes the NVP-CI and the TTRAM members should be thus replicated in an appropriate way also among the Workgroup components, since up to now, as showed in the patent foramen ovale (PFO) case study, only clinical specialists coming from different hospitals usually take part to the process. Of course, this doesn't mean that generalists should be involved, but domain professionals from different backgrounds, such as community representatives, finance and information staff, and academic researchers, who have expertise in the specific field of the technology under evaluation, should take active part in the Assessment process. First, their role consists in driving the literature search by suggesting specific keywords during databases'

consultation, while providing pertinent documentations and studies which can be directly screened by other components and strengthen the opinions they will uphold; second, they will be enabled to produce contributions for specific criteria and issues throughout the SIM editing, so that the right experts answer the right questions, unlike currently happens that often clinicians have to fill in economic or organizational points in the effort of depicting a complete overview about the technology of interest. As a matter of fact, today Assessment Coordinators for each evaluation match one or two dimensions to available experts according to their beliefs and common sense, sometimes without a defined rationale.

A more codified method to associate members to their specific area of participation is proposed in the following matrix, where the 21 criteria (in rows) are combined with related expert roles (in columns), namely specialist clinician/area nurse/health professional, epidemiologist/medical statistician, patients' association representative, and health economist/management engineer.

Criterion \ Expert role	Specialist clinician/Area nurse/Health professional	Epidemiologist/ Medical statistician	Patients' association representative	Health economist/ Management engineer
C1 – Completeness and consistency of documentation	✓	✓		✓
C2 – Relevance and validity of documentation	✓	✓		✓
C3 – Description and severity of illness	✓	✓	✓	
C4 – Size of population		✓		
C5 – General Healthcare Goals	✓	✓		
C6 – Description of technology and benefits areas	✓		✓	
C7 – Improvement of Safety and Tolerability	✓			
C8 – Improvement of Efficacy and Effectiveness	✓			
C9 – Improvement of patient related outcomes			✓	
C10 – Guidelines & good practice recommendations	✓		✓	
C11 – Limitations of alternative technologies in use	✓			
C12 – Financial Impact on Health system	✓			✓
C13 – Cost-effectiveness				✓
C14 – Impact on other spending	✓			✓
C15 – Impact on efficiency (cost-opportunity)	✓			✓
C16 – Impact on equity and accessibility	✓			
C17 – Coherence with national, regional planning				✓
C18 – Impact on healthcare needs	✓		✓	
C19 – Pressure of interest groups	✓		✓	✓
C20 – Historical and political context				✓
C21 – System capacity, appropriate technology use	✓		✓	✓

Table 6.4 - Combination criteria-expert roles

As showed, trans-disciplinary intersections are still present, as professionals have to find a proper ground of dialogue and comparison, however some of these roles are more predominant than other ones, however the possible composition of a Workgroup, which components are appointed and searched by NVP-CI members, couldn't be determined *a priori*, as a higher or lower number of experts to be involved in the evaluation is directly proportional to the available time and scheduling of different technologies, which are selected by the General Healthcare Directorate. In fact, one experts' groups couldn't undertake the evaluation of many technologies under comparison (for instance, this happens in case of different drugs which treat the same disease) in the same time employed by another equipotent experts' group assessing a technology with only one comparator. Thus, the dimension to take more into account could be the needed "full time equivalents", in order to better drive evaluations to reach "full speed" and provide fast response to proposed technologies.

Related implications for the Lombardy Region system entail the necessity of a more consistent commitment in scouting and enrolling the legitimate human resources in order to best fit with an evolving reality. Even though time constraints and experts' concerns about involvement of patients' organizations or other non specialists have often prevented the implementation of what is declared in the regional deliberation, each one has to gain equal right, upon communication and filtration of conflicts of interest, to broaden the perspective on the technology under evaluation and provide the final jury with a robust report which strengthens not only evidence based, but also trust based medicine.

R1. The panel of experts should include not only clinicians or health staff, but also properly selected patients' associations, health economists, and personnel with organizational competences, in order to take part to the elicitation of literature and to more effectively complete the SIM issues.

2. Does the TTRAM composition affect the usefulness of the MCDA Index? Should a proper balance of covered areas be reached in order to guarantee more reliability of results?

Two intertwined problems are to be discussed at this point: first, it's important that an equal composition of different TTRAM disciplines is reflected also in a corresponding significance on the final judgment, since the MCDA Index represents a composite appropriateness of use result; second, this makes sense only upon the joint agreement among all participants that the algorithm is useful to achieve a robust support for the final decision, thus referring back to the issue of engagement of TTRAM components which was previously delineated.

Since its first embrace by the Lombardy Region, the MCDA model was thought to be only a tool used to complete discussions and opinions aimed at reaching the final decision of the Appraisal jury, which could provide a tentative process formalization. What it should really be is, instead, an instrument which could strengthen decision making by analyzing more thoroughly what is at stake and leads to a certain well-reasoned choice. In fact, the MCDA criteria already represent a measurement tool for all the relevant considerations in the decision making process. Important criteria therefore depend on the decision making context. Once all possible choices have been evaluated on the basis of the selected criteria, they can be equitably compared and conclusions can be formulated. Thus, Multi-Criteria Decision Analysis is a transparent and explicit process which is aimed at including all considerations relevant to the decision that has to be made and providing sufficient clarity to ensure consistency in the translation of information into a final result (Mujoomdar, et al., 2012). The second issue, instead, is related to participation of stakeholders during this phase, as its current low level may be due to lack of a clear description of roles of tools and targets of the evaluation, to insufficient communication and comparison among the group members, to unclear definition of a methodological guide for using the internet portal, or to the necessity of more pressure by the General Healthcare Directorate on the participation to meetings.

Thus, the proposed points to be pondered refer, on the one hand, to the necessity of achieving an appropriate balance and expertise of different discipline areas in order to better legitimize the whole process, as every jury component has to give his/her approval. On the other hand, this is connected and further grounded in the utilization of the MCDA model not just as a simple information instrument, but also as an element of discussion and a reliable indicator of appropriateness, thus involving more actively participants in the overall decision making procedure, in order to also strengthen motivation deriving from the awareness of future impacts of their choice on normative regional measures.

Regarding the first point, literature is silent about the proper segmentation of the stakeholders' final roundtable group, as first experiences of the integration of Multi-Criteria Decision Analysis with priority setting in healthcare interventions developed not long time ago. When the multidisciplinary Appraisal committee shows areas not equally represented, usually a final discussion is performed and consensus is reached in order to grant each one the possibility to express his/her opinion. However, a different approach should consist not only in verbal agreement and reasoning, but also in the incorporation of the MCDA model, which will strengthen the appropriateness of use decision; in fact, weighted sums could be equally balanced according to the different represented groups before the final calculation, instead of conferring each one the same power, if a certain discipline, for

instance, is overrepresented among each others. Based on literature, the priority setting process should be strongly embedded in the organizational context, where the advisory panel comprises key stakeholders, as previously pointed out: the committee for the final decision may include not only those directly and indirectly involved in the programs being considered (doctors and managers for the former category, and collaborating providers, policy makers, finance and information staff for the latter one), but also the citizens' representatives, who have an important role in ensuring decisions reflect the community's values and needs (Peacock, et al., 2008), and haven't been included yet in the VTS Appraisal group. Furthermore, regarding the algorithm itself, compensatory rather than non-compensatory techniques seem apt as public decisions typically allow trade-offs between criteria (perhaps except in situations where ethical issues are central). Moreover, because of the need to rank order a large number of interventions rather than to identify a single (or small number of) dominant interventions, the linear additive model seems more suitable than other methods, by achieving a final index which enables technologies to be compared (Baltussen, et al., 2006).

Not only the composition of areas, but also the level of understanding of the process itself is a key question which provides more legitimization to the final decision: in fact, certainty of a good quality evaluation stands on a proper balance reached on the level of expertise of participants about health policies and decision making. The complexity of the appropriateness of use judgment can be better faced only when Appraisal components reach a mature reasoning which is based not on good sense, but on experiences they developed on the topic. This issue points out the necessity of changing also the approach of enrolling TTRAM members, who currently don't apply to participate to the process, but rather are appointed by Local Health Authorities, hospitals, foundations upon General Healthcare Directorate request: in order to guarantee a proper seniority for in-depth reasoning on relevant decisions, it's thus meaningful to compensate this practice with the possibility of self-application by professionals themselves.

Concerning the second point, when both weighting criteria and scoring options against those criteria, it is important to understand the real effect of what is being evaluating and to explore wide variations in responses, employing methods such as histogram-type presentation of weights/scores often associated with Delphi studies, rather than automatically concealing those variations by computing means. Discrepancies in the normative task of weighting criteria could indicate important differences in values, which should be explored rather than being concealed, while variations in rating options against criteria could result from differences in knowledge or expertise or from misunderstanding of the task being undertaken (Mullen, 2004), as previously demonstrated. However, effective communication of goals and open discussion of doubts among participants should be the first moves which guarantee their secure commitment during the whole process.

In fact, to the Lombardy Region framework, the increasing use of the decision making tool will guarantee more rationality, as the panel has an important role in making recommendations for reallocating resources on the basis of MCDA results; moreover, the primary focus lies on rendering the key determinants of decisions more explicit and accountable, by enhancing the quality of the “social intelligence” bearing on policy making, thereby assisting in better-informed and more technically robust, as well as more democratically accountable, science-policy outcomes (Burgess, et al., 2007). This recommendation represents just a first boost for the readjustment of the process itself: however, both instruments and framework are at their initial stage, thus improvements are still on their ongoing way.

R2. The TTRAM group should be well-balanced according to different areas and understanding of the process, while the MCDA Index should be taken into account as a means of legitimizing appropriateness of use judgment.

3. Is the VTS-HTA program sustainable over large scale evolution of the activity?

When thinking about the importance of reaching a balance between, on the one hand, a thorough analysis of evidence and context-based information in order to make the best judgment and, on the other hand, a fast decision making which is aimed at allocating scarce health resources, the scalability of the VTS program represents a challenge to be met and overcome to most effectively achieve an end result. Thus, a change has to be implemented, as the current practice resulted to have a low progress rate, which means that ongoing evaluations are too few, and the editing of the SIM during the Assessment phase is a time consuming process that in some cases represents only a bottleneck preventing the Appraisal final choice.

In technology assessment, the determination of concepts of HTA Doers and HTA Users started to develop a few years ago: specifically, these regard whether HTA organizations operate with the aim of carrying out the whole procedure by themselves, i.e. they specifically process the literature review and Assessment phase, thus creating a final HTA report, or they “outsource” this step by providing what have been already searched and assessed by other organizations, paying specific attention to a proper contextualization.

More specifically, a first definition is provided by the Age.Na.S., the National Agency for Regional Health Services, which characterizes HTA Doers as those organizations which (Cerbo, 2011):

- Perform an exhaustive collection of data through a relevant literature search (for instance, peer reviewed, unpublished);
- Undertake a critical and transparent appraisal of evidence;
- Formulate conclusions;
- Involve technology experts who revise the documentation in order to guarantee quality, accuracy and validity of the report.

Indeed, this is how the Lombard VTS process currently goes through the technology evaluations.

On the other hand, HTA Users are those organizations which characteristics are:

- Objectivity and awareness of the need for information about technologies prior to the decision;
- Clarity of health goals to be pursued;
- Integration of HTA in decision making processes;
- Awareness of HTA limitations;
- Auditing;
- Funding of activities.

Furthermore, HTA Users can be defined at the three levels, with different targets (Cerbo, 2011):

- Macro (central health authorities): to assess the impact of the technology progress in order to produce recommendations on use and diffusion;
- Meso (regions, hospitals, and Local Health Authorities): to drive their management choices about the use of the technology and its innovations;
- Micro (physician and/or health worker): to evaluate the opportunity of using the technology or its innovation on the single case basis.

Endorsed in these details, a new approach for the Lombardy Region VTS framework should take into account both practices with a long term view and a future change, for instance, from 20 to 50, 100 or even 200 evaluations per year: in fact, in the usual way though healthcare technology evaluations, specific documentation is searched, checked and integrated by experts, in order to provide a whole HTA report on a certain technology, drug or intervention, i.e. the structured multi-criteria assessment report. It's worth noting that, on the contrary, in other international experiences general HTA investigators perform the systematic review of literature to be handed to experts for efficient integration of evidence; however, this may not always guarantee a full view on the question of

interest, that's why the Assessment phase should be "sealed" by domain panelists and a proper division of tasks should be performed to better complete and validate the final document.

On the other hand, in those circumstances where detailed HTA reports on a specific technology are already available, maybe from other contexts or provided by other HTA organizations, panelists should decide whether to accept and endorse the report as it is, to update/upgrade the documentation available, or to undertake a full literature review if the information provided is considered to be poor. Anyway, in case of positive acceptance, panelists may add further contextualization details or their own contribution of expertise. It's important to note that this practice could be prevalent for those organizations where the yearly number of technology assessment requests is very high and there isn't enough time to perform a systematic review for each one of them.

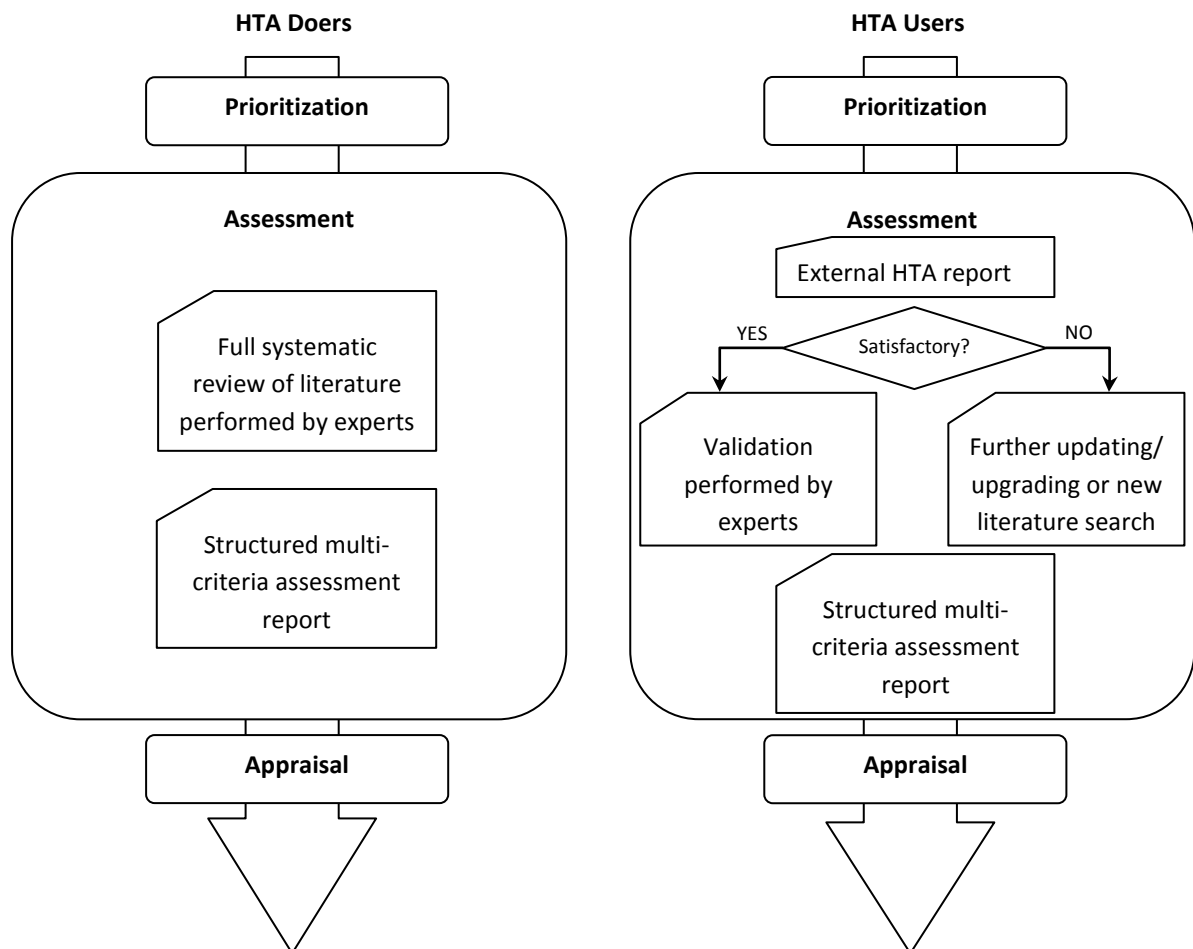


Figure 6.4 - HTA Doers' and Users' activities flow chart

In the above figure is thus provided the flow chart of HTA Doers' and Users' activities, paying particular attention that in the latter case the Assessment phase should still have an important task in validating the documentation to complete the SIM and to finally be handed to the Appraisal group: more specifically, the ad hoc certification of HTA reports performed by qualified experts should

always undertake, on the one hand, the “quality control” of used keywords, while, on the other hand, the addition of an essential element of contextualization which consists in the analysis of the regional Data WareHouse.

Furthermore, in case of necessity of revision of a certain decision, information available will be updated with the documentation of new evidence published and, according to this, panelists will decide whether to modify or not their current position on criteria (PNLG, 2002).

In a view of future necessity of making decisions as fast as a new request is presented to the NVP-CI members, the VTS framework has to provide a rapid response system: it should be taken into account that the goal of the process is not the production of an HTA report, for which purpose other organizations have been established, but a decision of appropriateness of use for a certain technology, thus adding contextualized recommendations. In fact, according to the degree of priority which is decided by the NVP-CI members, currently assessments have to be concluded in 4, 8 or 12 months; in an average situation, the workflow of activities could be detailed as follows:

- Prioritization phase: it could last approximately two months, where the first literature search, in order to edit the Rapid Report, the association of judgments on dimensions, and the experts’ search are the most time consuming activities, for which at least two weeks each are needed; in the should-be proposal, duration of this phase has to be shortened to one month, with proper training of components on methodologies for weighting and scoring and concurrent activities of literature’s and experts’ searches;
- Assessment phase: this is the longest procedure, as at least three months are needed to implement the systematic review of literature, the whole collection of both Evidence Base and Data WareHouse information, and the SIM editing by panelists. In the should-be approach, some activities have to be urged more effectively, in order to shorten the whole process and avoid waste of time: furthermore, when a complete HTA report is provided by experts or by the General Healthcare Directorate, fast validation of keywords and contents has to be performed, followed by the allocation of suggested scores, to reduce the process length to two-three weeks. In this case, the regional Data WareHouse analysis could be even started in parallel with the Prioritization phase, when a first description of the problem has been already identified, so that no further delays are present; this means that the Assessment phase should be however maintained with the role of validation, while experts represent official authority for the following decision;
- Appraisal phase: during the SIM editing, usually TTRAM members perform the anticipatory weighting of criteria, and only when the Assessment step is concluded scores are associated

to feed the Multi-Criteria Decision Analysis model; these activities last two months, as judgments have been showed to be difficult to collect, and the final discussion will have to wait long time. The new proposed approach would, on the contrary, shorten this last step to a maximum of three weeks length, with a twofold advantage: on the one hand, as already implemented, the anticipatory weighting of criteria should be put into practice in parallel with the Assessment phase and upon specific information on the policy question about the technology of interest, in order to avoid evaluation bias; on the other hand, scores, which have been suggested by experts, could be confirmed or confuted in a more straightforward way. This change will lead directly to the final discussion of the appropriateness of use indicator and the decision itself.

Hence, the embrace of a fast response method, which would solve the main bottleneck of current practice, will give more powerful and real effectiveness to the whole process: more specifically, at system's full operating speed, the Assessment step will serve as a robust step for studies' validation, by providing useful and usable documentation for the multidisciplinary jury which will decide how to appropriately allocate healthcare resources.

R3. The VTS program will have to clearly define in which situations is needed to develop a HTA report (HTA Doers), and when to endorse already available studies properly checked and validated (HTA Users). In order to make the process of technology evaluation faster, a structured protocol for the Assessment phase has to be detailed from the perspective of a future increase of requests.

Finally, if the whole process isn't transparent, policy goals may fail because the field community perceives them as ambiguous or illegitimate. Factual policy-making is a process of highly dynamic interaction between a large variety of stakeholders within a network of formal and informal relationships. To do justice to the multiplicity of different perceptions and often-conflicting interests of stakeholders, a model of policymaking should address the pluralism, dynamics and interdependences of such a network, rather than hide them (Bots, et al., 2000). Only in this way legitimate decisions are achieved, thus corroborated by appropriateness and reasonableness, which represent their authentic pillars.

7. Conclusions

7.1 Results Achieved and Lessons Learned

Overall, the present study points out the main criticalities emerged in the Lombardy Region context, which could be anyway exported to other backgrounds where similar models are implemented. As a matter of fact, comparison with other experiences is always a useful means for continuous improvement, since the core of HTA stays in corroboration and institutionalization of evaluation models through the creation of a community of knowledge generation and dissemination.

Thus, answers to research questions posed at the beginning of the study could be finally provided, by transparently clarifying the steps required for a new attitude towards improvement and renovation of current practice. Results accomplished follow the initial questions:

RQ1: Is the current architecture of the VTS-HTA model properly legitimized?

As shown in previous chapters, the present infrastructure of the VTS-HTA model has been **thoroughly legitimized** by first approaching to the basic principles of HTA, to international experiences, and their related decision making methodologies; the consequent step consisted in embracing and adapting these methods while putting forward contextualization aspects, in order to fit the specific regional background. This meant the standardization of three elements, i.e. the model, the actors and the process itself, which are aimed at ensuring a definite level of rationality and equity.

Furthermore, the objectives fulfilled could be described as follows:

- The **model**, which consists in the operationalization of the EUnetHTA Core Model for issues and topics, and the inclusion of EVIDEM criteria for the Multi-Criteria Decision Analysis implementation, can be considered complete and consistent with the dimensions of evaluation needed to make a comprehensive decision;
- The **actors** involved cover different scientific areas, such as required by the HTA perspective; roles of evaluation bodies are properly defined, however with some differences from the EVIDEM framework: for instance, in the Canadian model only experts are involved in the evaluation of the documentation and the subsequent weighting and scoring of evidence, while in the current Lombardy VTS-HTA model the TTRAM group will evaluate the document provided by the Assessment experts;
- The **process** has been grounded in the NICE methodology, which includes the phases of Prioritization, Assessment and Appraisal, thus a logical workflow of activities is conceived in

order to generate the best outputs for the final judgment of appropriateness of use for the technology.

RQ2: Is the current process efficient in order to guarantee a straightforward and transparent functioning from the perspectives of exchanges of information and organizational structure?

As shown in the PFO case study, both the amount of information to manage, and the organization of the Assessment panel of experts present some **difficulties** which prevent a plain progress of the evaluation, thus **limiting its efficiency**.

In fact, on the one hand the analyzed **activities** resulted to be inflexible and **over-structured** when dealing with the necessity of collecting information and selecting appropriate documentation to complete the SIM issues: for instance, many of the present questions usually can't be answered due to lack of information and of expertise of selected members. This will prevent the following Appraisal step to reach an overall opinion on the technology. On the other hand, the **multidisciplinary composition** of groups showed to be **incomplete**, as lacking information could be better collected by involving qualified components who lie outside of the clinical background. Furthermore, this is also connected with the Appraisal phase, which is affected by low participation issues: a definite appropriateness of use judgment can't be reached by the final jury without a proper link between the complete gathering of documentation and the thorough understanding of what this activity is aimed at.

The efficiency of the decision making process is also defined by its specific **timing**, as HTA revealed itself to be time consuming, and often a full HTA evaluation could result inconsistent with the need for assessing numerous requests within budget constraints: even though more urgency has to be put into current practice, as turnover of healthcare technology innovations changes fast, frequency of final decisions has to be well-balanced with quality and appropriateness of evaluation themselves. This recalls the importance of a connected accomplishment of equilibrium in the organizational structure: in fact, what should be improved in current practice is knowledge of the process to which actors have to actively participate and, most of all, of its real capabilities; only thanks to a proper information about the actual contribution rising from the achievement of the target, actors will feel more intensely involved in the definition of the final decision (Arioli, 2012). Thus, not only owning the decision options, but also knowing the consequences of a certain choice are necessary to make healthcare planning more robust, coherent, transparent and verifiable.

However, the demand for constructive benchmarking with other organizations and sustainable activities move necessarily towards a transformation of the as-is framework, which is expressed in the next answer.

RQ3: What are the main levers driving an effective improvement of both design and management structure of the process?

Current issues which were detected in the previous chapter could be overcome thanks to a well-reasoned **breakdown of elements** which compose both the methodological tool and the organizational configuration, in order to propose **“ready-for-use” recommendations**. As the as-is process showed weaknesses in these two pillars, criteria, weights and scores were to be discussed in the first stream, while group composition, usability and sustainability of the system in the second one; proposed changes have a certain level of attainability (e.g. high, medium, or low) for the Lombardy Region organization, to which a major or minor effort in terms of fast response is required.

SHOULD-BE	Level of Attainability of the Proposal
MCDA issues	
R1. Scores, which represent the performance of the technology under evaluation related to the different criteria, should be first suggested by Assessment experts themselves, who express a “univocal utility function” that is directly connected to both their literature review and their knowhow, in order to provide a first orientation for TTRAM members and further engage them in a better understanding of the SIM.	Medium: as this represents a conceptual change of current practice, Assessment experts and TTRAM members have to be methodologically trained in order to best align their process understanding and engage to their tasks; this may entail a higher effort as experts become more responsible for their analyses and TTRAM more active in their relevant role of final jury.
R2. C1 and C2 should be separated from other criteria, since their evaluation is already implied when rating other criteria themselves;	High: this separation of activities is straight, however modifications of the framework for evaluating evidence have a low level of urgency.
r3. Overlapping issues should be eliminated in order to make the asking and answering process leaner and more understandable with mutually exclusive information.	High: a proper selection of non-overlapping issues can be easily performed in order to consistently collect information.
r4. The weights could be freely associated to criteria with the allocation of 100 points.	High: this minor recommendation allows more independence, but upon pondered judgment.
R5. Weights should be maintained different in order to avoid bias which may occur if the specific context is not thoroughly taken into account.	High: the establishment of a certain level of communication among TTRAM members will enable effective allocation of weights during each evaluation.
Organizational Structure issues	
R1. The panel of experts should include not only clinicians or health staff, but also properly selected patients’ associations, health economists, and personnel with organizational competences, in order to take part to the elicitation of literature and to more effectively complete the SIM issues.	Medium: even though pressures from the other international practices may start to move the current approach towards a broader perspective, it is important to clearly define a protocol for selecting qualified members.
R2. The TTRAM group should be well-balanced according to different areas and understanding of the process, while the MCDA Index should be taken into account as a means of legitimizing appropriateness of use judgment.	High: rationality is easily corroborated by a proper definition of targets and an exemplification of procedures and tools to be used to increase personal sense of responsibility.
R3. The VTS program will have to clearly define in which situations is needed to develop a HTA report (HTA Doers), and when to endorse already available studies properly checked and validated (HTA Users). In order to make the process of technology evaluation faster, a structured protocol for the Assessment phase has to be detailed from the perspective of a future increase of requests.	Medium: as the main bottleneck of the process is efficient and effective decision making, this change may entail a longer time before being naturally incorporated in “daily routine”, however it should be taken into account that the main objective doesn’t reside in the redaction of a HTA report, but in the decision for appropriateness.

Table 7.1 - Recommendations and related Levels of Attainability for Lombardy Region

As depicted in table 7.1, different solutions proposed may imply distinct levels of applicability: on the one hand, the **Multi-Criteria Decision Analysis model** still moves a long debate about whether its components should be considered reliable to reach a final decision or it is only a support on which basing first reflections. However, besides its level of integration into the decision making process, it's important that an **in-depth understanding of both roles of single steps and targets** which they will score is present among all the participants involved; in fact, current methodological developments increase complexity of the analysis at the expense of transparency, and may, in some cases, ultimately lead to inefficient resource allocation (Brousselle, et al., 2011). Furthermore, the element of contextualization is important in order to complete a broad overview on the technology of interest. Thus, the biggest challenge is not to find information, but rather to develop the capacity to use HTA information (WHO, 2011), as it has to be codified in the correct way by actors involved who will produce a robust and reliable final decision. In this sense, the Multi-Criteria Decision Analysis should represent a first step moving a thorough reflection on the necessary and sufficient information for healthcare technology priority setting and appropriateness of use decision: not only what has been well documented, but also what provides improved value in health has to be taken into account in order **to guarantee more credibility of the healthcare system in the long run.**

On the other hand, regarding the **organizational structure**, it was shown that a **thorough awareness of direct impacts of choices** may help stakeholders to better focus on the achievement of their targets, enable scenario building and actually quantify effects of policy on determinants of health: as causal pathways are drawn, in fact, barriers and inconsistencies could be overcome, in order to directly provide reasons for reallocation of resources, disinvestment, or, for instance, the necessity of establishing registries which drive medical practice and clarify guidelines that should be followed; in particular, a reflection for validation regarding this discussion was undertaken with Coordinators of the Patent Foramen Ovale (PFO) evaluation and is available in Annex F. Impacts of decision making affect different spheres, such as patient, technology, economics, organizational system and public context, thus synergies, which are corroborated by the presence of relevant evidence, have to be created to support effective and useful decision making. Thus, different roles, belonging to various fields of science, are needed to reach the most exhaustive overview on the technology under evaluation: this is not only a matter of specific knowledge on the topic itself, but also of peculiar capacities of reporting possible inconsistencies or methodological gaps and thorough reasoning on the process in order to provide a mature judgment on health policies. A progressive strategy, with the attendance to workshops in order to become familiar with concepts, methods and results of HTA, and the participation in HTA policy networks, could, hence, disseminate knowledge and improve practical skills.

Finally, this research highlights crucial points of consolidation towards which the current practice has to move, as this **novel proposed approach** is not based only on the necessity of a different mindset, but also on the creation and exploitation of **enabling factors** which emerge through the **analysis of methodological tools** and the **proper engagement of actors**. The in-depth understanding of causes and impacts of choices on the healthcare system should instill a even **higher sense of responsibility** in both experts and final decision makers about what is being implemented. In fact, although stakeholders, who still are human beings subjected to potential mistakes, may entail drawbacks and limitations of decision making procedures, changing practice of both knowledge management and sharing is as crucial as mandatory (Nielsen, 2012), in order to clearly redefine targets for sustainable healthcare from a multidisciplinary perspective. Moreover, the constructive comparison and rethinking on models of other international organizations Lombardy Region collaborates with, results to be useful in a long term attitude of engagement for appropriate, robust and responsible choices.

7.2 Limitations

This research presents some limitations that will be deepened in further studies: the first point is related to the complexity itself of the issue of finding the best way to improve current decision making. Since often availability of comprehensive high quality data is problematic, actors involved into the process should find with their own approach the best optimization for necessary information, in order to provide legitimate and contextualized final decisions. In fact, as shown in the previous chapters, the structural elaboration of the Lombardy VTS-HTA framework presents different backgrounds, instruments and roles which are still organized in a heterogeneous way, so that focusing on a certain point wasn't possible.

The second limitation is then correlated to features of a still ongoing process which is taking its first steps and will be implemented at full speed, thus the necessity of field testing would be a sound solution to highlight both its upsides and downsides, while finally preventing possible inconsistencies and finding a composite direction for improvement. This sharply limited the possibilities of controlling and confirming recommendations proposed in the final chapter, except for an initial feedback provided by the General Healthcare Directorate and a partial contribution added by Coordinators of the technology evaluation which could be followed in its distinct stages. As previously reported, proposed advices are expressed in a "should-be", and not "to-be" form, in order to point out their function of early signals to be taken into account and the related necessity of meeting contextualized emerging requisites in order to accomplish efficient and effective process refinement. Qualitative and quantitative contributions are needed, nevertheless these observations

targeting both methodology and organizational structure are the first fundamental aspects to be questioned.

Besides these limitations, this study presents major and minor recommendations which were directly inferred from issues that lie at the heart of the HTA process; furthermore, a sustainable decision making system could be only achieved with context based engagement and improvement of shared practice.

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Annexes

A. NICE Guidance

A standard NICE guidance is developed after careful consideration of available evidence in order to provide useful information for healthcare professionals when exercising their clinical judgment. However, the guidance doesn't override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. Implementation of each guidance is the responsibility of local commissioners and/or providers, who are reminded that it is their responsibility to implement it in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality and opportunity.

The basic framework is structured with the following paragraphs (NICE, 2009):

1. Guidance: recommendations about the use of the technology and the steps to implement before the decision of undertaking a procedure;
2. Clinical need and practice: information regarding the target disease, the affected population and the current standards of managing the condition;
3. The technology: it includes specific details on how the intervention is implemented and which instrumentation is needed;
4. Evidence and interpretation: details about the Appraisal Committee and sources of evidence regarding these topics:
 - a. Clinical effectiveness from systematic reviews, taking into account comparisons of different treatments and risk factors' assessment;
 - b. Cost-effectiveness from economic evaluations of published literature and manufacturers' economic models;
 - c. Consideration of the evidence and comments;
5. Implementation: regarding how and why each guidance can be implemented;
6. Recommendations for further research
7. Related NICE guidance
8. Review of guidance: related to the further examination and updating of the current guidance (usually after three years).

B. EUnetHTA Core Model Element Card and Assessment Element Examples

Empty Element card

Element ID:		
Domain:	☐ Health problem and current use of technology ☐ Description and technical characteristics ☐ Safety ☐ Accuracy ☐ Clinical effectiveness ☐ Economic evaluation ☐ Ethical analysis ☐ Organisational aspects ☐ Social aspects ☐ Legal aspects	
Topic:		
Issue:		
Clarification:		
Importance:		Explanation:
	☐ Critical	<i>Should always be considered in an HTA</i>
	☐ Important	<i>Should be considered in most HTAs</i>
	☐ Optional	<i>May provide useful information</i>
	Specific requirements for importance:	
Information source(s):		
Transferability:		Explanation:
	☐ Complete	<i>Data/findings are context independent</i>
	☐ Partially	<i>Data/findings are not directly transferable from one setting to another. Adjustments are needed.</i>
	☐ Not	<i>Data/findings are not transferable from one setting to another without serious difficulties.</i>
Reference:		
Relations:		
Status:		Explanation:
	☐ Core	<i>Belongs to core.</i>
	☐ Borderline	<i>May belong to core. (Comment: need to discuss whether this category is needed).</i>
	☐ Not Core	<i>Does not belong to core. Part of wider HTA framework.</i>

Assessment element: *Domain Safety*

ID	Topic	Issue	Clarification	Information sources
C0001	Patient safety	What kind of harms can use of the technology cause to the patient and what is the incidence, severity and duration of harms?	Are the harms intrinsic to the technology (primary effect) or application dependant (secondary effects) or an unrelated event consequent on its use?	
C0002	Patient safety	What is the dose relatedness of the harms to patients?	Here one should consider also the accumulated harm due to repeated testing.	Research articles, manufacturers' product data sheets, safety monitoring databases.
C0003	Patient safety	What is the timing of onset of harms to patients: immediate, early or late?	The onset of the harm will be different dependant on the mechanism of action and type of technology. Some harms may not be detected because the duration of follow up is not sufficiently long.	Manufacturers/ medical literature/ grey literature/ registries/ national or international safety monitoring systems
C0004	Patient safety	Is the incidence of the harms to patients likely to change over time?	For some technologies the occurrence of harms may change over time and be dependent on the experience or training of the operator?	Medical literature/ grey literature/ professional societies/ registries
C0005	Patient safety	Are there susceptible patient groups that are more likely to be harmed through use of the technology?		Research articles, manufacturers' product data sheets, safety monitoring databases
C0006	Patient safety	What are the consequences of false positive, false negative and incidental findings brought about using the technology to the patients from the viewpoint of patient safety?		Research articles
C0007	Patient safety	What are the special features in using (applying/interpreting/maintaining) the technology that may increase the risk of patient safety?	Is there evidence for operator dependent harms? Is there a learning curve and what is its consequence? Is there is a big intra- or inter-observer variation in the reading of test results, what is its consequence?	Research articles, manufacturers' product data sheets, safety monitoring databases
C0008	Patient safety	What is the safety of the technology in comparison to alternative technologies used for the same purpose?	Relative impact of harms comparative to alternative treatment(s) for individual patients, populations, service delivery & cost	Other HTA reports or systematic reviews of main comparators. Manufacturer or

			effectiveness	regulators information
C0020	Occupational safety	What kind of occupational harms may exist through using the technology?		Research articles, manufacturers' product data sheets, safety monitoring databases
C0040	Environmental safety	What kind of environmental risks may use of the technology cause?		Research articles, manufacturers' product data sheets, safety monitoring databases
C0060	Safety risk management	How does the safety profile of the technology vary between different generations, versions or products?		Research articles, manufacturers' product data sheets, safety monitoring databases
C0061	Safety risk management	Is there evidence that harms increase or decrease in different organizational settings?		Accuracy and effectiveness research, epidemiological risk research
C0062	Safety risk management	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?	Is there a requirement for specific training, use of a protocol or guideline or restricting use to specialist centres, providing patient information, etc. may all reduce the occurrence or severity of harm.	
C0063	Safety risk management	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?		Research in occupational health and safety
C0064	Safety risk management	How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)?		Research articles, manufacturers' product data sheets



CARTA DI TRENTO

sulla valutazione delle tecnologie sanitarie in Italia

LE PREMESSE

Il concetto di tecnologia sanitaria è ampio e comprende le attrezzature sanitarie, i dispositivi medici, i farmaci, i sistemi diagnostici, le procedure mediche e chirurgiche, i percorsi assistenziali e gli assetti strutturali, organizzativi e manageriali nei quali viene erogata l'assistenza sanitaria. Le tecnologie sanitarie comprendono quindi tutte le applicazioni pratiche della conoscenza che vengono utilizzate per promuovere la salute e prevenire, diagnosticare e curare le malattie.

La valutazione delle tecnologie sanitarie è di conseguenza la complessiva e sistematica valutazione multidisciplinare (descrizione, esame e giudizio) delle conseguenze assistenziali, economiche, sociali ed etiche provocate in modo diretto e indiretto, nel breve e nel lungo periodo, dalle tecnologie sanitarie esistenti e da quelle di nuova introduzione. Tradizionalmente, essa rappresenta il ponte tra il mondo tecnico-scientifico e quello dei decisori.

A livello internazionale, la valutazione delle tecnologie sanitarie è una pratica diffusa da decenni. La Rete internazionale delle agenzie di valutazione delle tecnologie sanitarie (International Network of Agencies for Health Technology Assessment - INAHTA) raccoglie le decine di organizzazioni che nel mondo si occupano in modo specifico e sistematico di questo tema. La Società internazionale di valutazione delle tecnologie sanitarie (Health Technology Assessment International - HTAi) collega sul piano professionale tutti coloro che si occupano di questo tema nelle università, nei sistemi sanitari, nell'industria e nel volontariato. La Commissione Europea ha più volte riconosciuto l'importanza della valutazione delle tecnologie sanitarie ed è quindi nata la Rete Europea per la valutazione delle tecnologie sanitarie (European Network for Health Technology Assessment - EUnetHTA), che coordina gli sforzi di 35 organizzazioni europee.

Le esperienze italiane di valutazione delle tecnologie sanitarie si sono sviluppate solo negli ultimi anni e non esiste una specifica agenzia nazionale di valutazione delle tecnologie, anche se molte attività vengono comunque svolte da singole organizzazioni, nazionali, regionali o locali, che si trovano di fronte alla necessità di decidere se introdurre o meno nuove tecnologie sanitarie. Nel 2003, sulla base di un Progetto finanziato dal Ministero della salute, è stato costituito il Network Italiano di Health Technology Assessment (NI-HTA).

I PRINCIPI

Sulla base delle premesse citate, le organizzazioni aderenti al Network Italiano di Health Technology Assessment (NI-HTA), al termine di un processo di consultazione che ha coinvolto i partecipanti al "1° Forum italiano per la valutazione delle tecnologie sanitarie" organizzato a Trento dal 19 al 21 gennaio 2006 dall'Azienda Provinciale per i Servizi Sanitari di Trento, dall'Università di Trento e dal Network Italiano di Health Technology Assessment, concordano sui seguenti principi:

1. la valutazione delle tecnologie sanitarie deve coinvolgere tutte le parti interessate all'assistenza sanitaria;	CHI
2. la valutazione delle tecnologie sanitarie deve riguardare tutti gli elementi che concorrono all'assistenza sanitaria;	COSA
3. la valutazione delle tecnologie sanitarie deve riguardare tutti i livelli gestionali dei sistemi sanitari e delle strutture che ne fanno parte;	DOVE
4. La valutazione delle tecnologie sanitarie deve essere un'attività continua che deve essere condotta prima della loro introduzione e durante l'intero ciclo di vita.	QUANDO
5. la valutazione delle tecnologie sanitarie è una necessità e una opportunità per la governance integrata dei sistemi sanitari e delle strutture che ne fanno parte;	PERCHÉ
6. la valutazione delle tecnologie sanitarie è un processo multidisciplinare che deve svolgersi in modo coerente con gli altri processi assistenziali e tecnico-amministrativi dei sistemi sanitari e delle strutture che ne fanno parte.	COME

1 La valutazione delle tecnologie sanitarie deve coinvolgere tutte le parti interessate all'assistenza sanitaria

Le parti interessate sono le persone o i gruppi che hanno un interesse nelle prestazioni o nel successo di qualsiasi organizzazione, pubblica e privata, e vengono normalmente classificate in 5 categorie: i clienti, il personale, i proprietari/finanziatori, i fornitori e la società.

Le parti interessate all'assistenza sanitaria sono numerose: i malati e le loro famiglie, i professionisti e le loro organizzazioni scientifiche e sindacali, i rappresentanti dei cittadini ai vari livelli istituzionali e i contribuenti, le strutture sanitarie e socio-sanitarie, i partner commerciali e non profit che forniscono beni e servizi, l'industria, l'università, le associazioni di volontariato e numerosi altri soggetti ancora.

Le esigenze e le aspettative delle parti interessate all'assistenza sanitaria si combinano in modo diverso lungo le tre dimensioni fondamentali dell'assistenza: professionale, organizzativa e relazionale. Su alcuni temi le parti interessate hanno esigenze e aspettative comuni: per esempio, l'efficacia, l'appropriatezza e la sicurezza delle prestazioni. In altri temi, invece, le esigenze e aspettative delle parti interessate divergono: per esempio, i costi, la diffusione delle attrezzature e gli assetti organizzativi. Infine, le parti interessate hanno diverse capacità di percepire le esigenze e aspettative complessive e attribuiscono loro valori che dipendono dai rispettivi universi simbolici di riferimento.

La valutazione delle tecnologie sanitarie è un'occasione strutturata di incontro tra le diverse esigenze e aspettative delle parti interessate, che ne consente il successivo bilanciamento su criteri espliciti e condivisi tra le parti stesse.

2 La valutazione delle tecnologie sanitarie deve riguardare tutti gli elementi che concorrono all'assistenza sanitaria.

L'assistenza sanitaria è il risultato sinergico di molte tecnologie sanitarie, che possono essere materiali e immateriali.

Tra le tecnologie sanitarie materiali vanno considerati le strutture edilizie (gli ospedali, gli ambulatori, i domicili dei pazienti, ecc.), le grandi e le piccole attrezzature, gli impianti tecnologici e i variegati mondi dei dispositivi medici e delle sostanze chimiche (i farmaci, i vaccini, i sistemi diagnostici, ecc.).

Tra le tecnologie sanitarie immateriali vanno invece considerati i modelli organizzativi e assistenziali (pubblico/privato, assistenza ospedaliera/assistenza domiciliare, dipartimenti/servizi, degenza ordinaria/day hospital, ecc.), i documenti di indirizzo clinico (procedure, linee guida, percorsi assistenziali, modelli di appropriatezza, ecc.) e i sistemi regolatori (nomenclatori delle prestazioni, sistemi tariffari, procedure di autorizzazione e accreditamento, ecc.).

Tutte queste tecnologie sanitarie non sono efficaci di per se stesse, ma sono strumenti in mano alle persone, in primo luogo ai professionisti clinici e organizzativi che danno forma e vita alle strutture sanitarie.

3 La valutazione delle tecnologie sanitarie deve riguardare tutti i livelli gestionali dei sistemi sanitari e delle strutture che ne fanno parte.

L'assistenza sanitaria organizzata è il frutto di scelte che avvengono a diversi livelli decisionali.

C'è un primo livello generale, costituito dalle scelte legislative e dalle decisioni degli organismi di regolazione nazionale e regionale come, per esempio, il Ministero della salute, l'Agenzia italiana per il farmaco, l'Agenzia per i servizi sanitari regionali, l'Istituto superiore di sanità, gli Assessorati regionali alla salute e le corrispondenti Agenzie regionali. Queste scelte riguardano soprattutto l'accessibilità alle prestazioni, gli assetti organizzativi generali, i sistemi tariffari, la collocazione delle grandi apparecchiature e la presenza delle tecnologie nel mercato.

A livello intermedio si collocano le scelte gestionali proprie del management delle singole strutture sanitarie: acquisire o meno una certa attrezzatura, strutturare i percorsi assistenziali, adottare specifici assetti organizzativi, erogare o meno una prestazione assistenziale, ecc..

A livello professionale ci sono infine le scelte compiute dai singoli nella pratica assistenziale quotidiana: la scelta di un esame diagnostico, l'indicazione di un farmaco, la richiesta di una consulenza specialistica, la gestione di un piano di assistenza, ecc..

4 La valutazione delle tecnologie sanitarie deve essere un'attività continua che deve essere condotta prima della loro introduzione e durante l'intero ciclo di vita.

La valutazione deve riguardare l'impatto complessivo provocato dalle tecnologie sanitarie. Normalmente, la valutazione dell'impatto di una nuova tecnologia deve essere fatta prima della sua introduzione nella pratica quotidiana. Tuttavia, la valutazione deve essere fatta anche durante il normale periodo di utilizzo delle tecnologie, per dare assicurazione alle parti interessate che l'impatto reale sulle diverse dimensioni considerate continua a essere coerente con quanto previsto, anche a fronte degli inevitabili cambiamenti scientifici, tecnici, organizzativi, epidemiologici e di scenario.

5 La valutazione delle tecnologie sanitarie è una necessità e una opportunità per la governance integrata dei sistemi sanitari e delle strutture che ne fanno parte.

I sistemi sanitari e le strutture che ne fanno parte sono oggi stretti tra spinte contrapposte in rapida trasformazione: la transizione epidemiologica, l'evoluzione demografica, lo sviluppo tecnologico, la congiuntura economica e la crescita culturale della comunità.

La sostenibilità complessiva dell'assistenza sanitaria organizzata e la responsabilità di assicurare servizi efficaci sul piano professionale, efficienti su quello organizzativo, equi e rispettosi nei confronti dei cittadini impone che le tecnologie sanitarie vengano scelte attraverso un processo partecipato.

La valutazione delle tecnologie sanitarie è anche una opportunità per le strutture sanitarie perché l'esame multidimensionale dell'impatto provocato dalle tecnologie crea i presupposti per superare l'autoreferenzialità e l'isolamento nelle scelte, soprattutto in quelle che hanno conseguenze sui versanti etico e sociale. Inoltre la condivisione delle valutazioni svolte dalle singole strutture rappresenta un arricchimento per il sistema sanitario nel suo complesso.

Anche sul versante interno la valutazione delle tecnologie sanitarie rappresenta una opportunità per le strutture sanitarie, perché integra in un disegno unitario le diverse professionalità presenti (i clinici, i tecnici, gli amministratori, gli organizzatori) e consente di governare fin dall'inizio la curva di adozione delle tecnologie.

6 La valutazione delle tecnologie sanitarie è un processo multidisciplinare che deve svolgersi in modo coerente con gli altri processi assistenziali e tecnico-amministrativi dei sistemi sanitari e delle strutture che ne fanno parte.

I sistemi sanitari e le strutture che ne fanno parte sono sistemi complessi, basati su una rete di processi assistenziali e tecnico-amministrativi lungo la quale i professionisti clinici e organizzativi e i cittadini si muovono con competenze, autonomie, responsabilità e percezioni diverse.

La valutazione delle tecnologie sanitarie è uno di questi processi ed è necessario che essa si snodi in modo coerente con gli altri: per esempio, con la gestione della sicurezza dei pazienti e dei lavoratori, con l'erogazione delle prestazioni, con il ciclo di vita delle attrezzature, con l'apertura o la chiusura delle attività assistenziali. Un elemento chiave è dato dalla formazione delle parti interessate, che deve coinvolgere non solo i professionisti ma anche i responsabili delle organizzazioni sanitarie e i rappresentanti dei cittadini.

La valutazione delle tecnologie sanitarie è quindi uno degli aspetti della gestione per la qualità dei sistemi sanitari e delle strutture che ne fanno parte, per accrescere la loro capacità di soddisfare le esigenze e le aspettative delle parti interessate.

Elementi essenziali per la credibilità delle valutazioni e per la loro sostenibilità di fronte alla parti interessate sono il coinvolgimento delle parti stesse, la piena adesione al metodo scientifico, l'approccio multidisciplinare e il rispetto dei principi di equità e trasparenza.

LE CONCLUSIONI

Le organizzazioni aderenti al Network Italiano di Health Technology Assessment (NI-HTA) propongono questi principi sulla valutazione delle tecnologie sanitarie nella consapevolezza che è necessario un grande sforzo congiunto tra tutte le parti interessate per governare il tema delle tecnologie in sanità. Auspicano che tali principi possano trovare spazio nei comportamenti e nelle scelte di tutti coloro che nutrono interessi nell'assistenza sanitaria e che il Network Italiano diventi lo strumento per collegare tra di loro le diverse esperienze che via via matureranno in Italia.

Trento, 28 marzo 2006



REPUBBLICA ITALIANA

Regione Lombardia

BOLLETTINO UFFICIALE

MILANO - MARTEDÌ, 2 SETTEMBRE 2008

1° SUPPLEMENTO STRAORDINARIO

Sommario

C) GIUNTA REGIONALE E ASSESSORI

Deliberazione Giunta regionale 30 luglio 2008 - n. 8/7856 (3.2.0)
Determinazione in merito alla valutazione dell'appropriatezza d'uso di farmaci, dispositivi
biomedici e tecnologie diagnostico-terapeutiche al fine del loro impiego nell'ambito del Ser-
vizio Sanitario Regionale secondo gli indirizzi del PSSR e determinazioni conseguenti .

3

Anno XXXVIII - N. 182 - Poste Italiane - Spedizione in abb. postale - 45% - art. 2, comma 20/b - Legge n. 662/1996 - Filiale di Varese

C) GIUNTA REGIONALE E ASSESSORI

(BUR2008031)

(3.2.0)

D.g.r. 30 luglio 2008 - n. 8/7856

Determinazione in merito alla valutazione dell'appropriatezza d'uso di farmaci, dispositivi biomedici e tecnologie diagnostico-terapeutiche al fine del loro impiego nell'ambito del Servizio Sanitario Regionale secondo gli indirizzi del PSSR e determinazioni conseguenti

LA GIUNTA REGIONALE

Visti:

- il d.lgs. 502/92 e s.m.i., con particolare riferimento all'art. 12-bis commi 4, 5, 6, relativi ai programmi di ricerca sanitaria;
- il d.lgs. 14 dicembre 1992, n. 507 «Attuazione della Direttiva 90/385/CEE concernente il ravvicinamento delle legislazioni degli Stati Membri relative ai dispositivi medici impiantabili attivi»;
- il d.lgs. 24 febbraio 1997, n. 46 «Attuazione della Direttiva 93/42/CEE concernente i dispositivi medici»;
- il d.lgs. 8 settembre 2000, n. 332 «Attuazione della Direttiva 98/79/CEE relativa ai dispositivi medico-diagnostici in vitro»;
- il d.lgs. 6 aprile 2005, n. 67 «Attuazione della Direttiva 2003/32/CE concernente i dispositivi medici fabbricati con tessuti di origine animale»;
- il d.m. del 22 settembre 2005 «Classificazione Nazionale dei Dispositivi Medici (CND)»;
- il d.lgs. 24 aprile 2006, n. 219 «Attuazione della Direttiva 2001/83/CE (e successive direttive di modifica) relativa ad un codice comunitario concernente i medicinali per uso umano, nonché della Direttiva 2003/94/CE»;
- il decreto del Ministero della Salute del 20 febbraio 2007 «Approvazione della Classificazione Nazionale dei dispositivi medici (CND)»;
- il d.lgs. 29 dicembre 2007, n. 274 «Disposizioni correttive al d.lgs. 24 aprile 2006, n. 219, recante attuazione della Direttiva 2001/83/CE relativa ad un codice comunitario concernente medicinali per uso umano»;

Richiamati:

- la d.g.r. n. 7/7197 del 3 dicembre 2001 «Valutazione delle tecnologie innovative in campo sanitario al fine del loro utilizzo nell'ambito del Servizio Sanitario Regionale»;
- il decreto del Direttore Generale Sanità n. 9900/2006 «Adozione Linee di indirizzo in merito alle modalità di verifica e controllo dei consumi farmaceutici»;
- il Piano Socio Sanitario Regionale 2007-2009 approvato con d.c.r. n. VIII/257 del 26 ottobre 2006;
- la d.g.r. n. 8/5743 del 31 ottobre 2007 «Determinazioni in ordine alla gestione del Servizio Socio Sanitario Regionale per l'esercizio 2008» (di concerto con l'Assessore Abelli);

Confermata la necessità stabilita dal PSSR al punto 5.1 di valutare l'efficienza e l'appropriatezza specifica delle tecnologie in ambito sanitario, nel rispetto dell'erogazione dei Livelli Essenziali di Assistenza (LEA);

Ritenuto che a decorrere dall'anno 2008 il contributo per gli obiettivi PSSR riconosciuto alle aziende pubbliche deve tenere obbligatoriamente conto della reale produzione delle attività di ricovero e di specialistica a contratto;

Dato atto che la d.g.r. n. 8/5743 del 31 ottobre 2007, con particolare riferimento all'allegato 8, prevede la possibilità che, sulla base delle modalità operative stabilite dalla d.g.r. 7/7197 del 3 dicembre 2001 «Valutazione delle tecnologie innovative in campo sanitario al fine del loro utilizzo nell'ambito del Servizio sanitario regionale», potranno essere promossi nel corso del 2008 dei progetti, prioritariamente nel campo della terapia del dolore e della interventistica cerebrocardiovascolare, per un valore complessivo regionale non superiore a C 5 milioni che, per quanto riguarda la parte di finanziamento regionale, saranno coperti dalla quota contrattata dalla struttura con la ASL di riferimento;

Valutato:

- di rivedere ed aggiornare gli strumenti indicati dalla predetta d.g.r. n. 7/7197 del 3 dicembre 2001 «Valutazione delle tecnologie innovative in campo sanitario al fine del loro utilizzo nell'ambito del Servizio sanitario regionale», messi a disposizione dell'amministrazione Regionale che permettano di affrontare in modo corretto le esigenze poste dalle tecnologie innovative in ambito sanitario;
- di facilitare la diffusione nella pratica clinica delle tecnologie più «efficaci, sicure ed efficienti» in sostituzione di tecnologie meno «efficaci, sicure ed efficienti», secondo modalità responsabili, condivise, trasparenti, monitorabili e verificabili, nel rispetto dell'erogazione dei Livelli Essenziali di Assistenza;

Ritenuto prioritario valutare quelle tecnologie innovative in campo sanitario che abbiano già concluso, in base alle normative vigenti, l'iter di sperimentazione clinica e che siano già in possesso dei certificati di autorizzazione all'immissione in commercio ovvero del marchio CE, secondo le dimensioni:

- della documentazione di efficacia (raggiungimento di risultati dimostrabili mediante evidenze scientifiche in termini di riduzione, in comparazione con standard appropriati, di recidive e/o di morbosità e/o di morbidità e/o di mortalità e/o di maggiore sicurezza);
- dell'efficienza allocativa delle risorse e dell'efficienza tecnica ed equità nell'erogazione dei servizi sanitari;

Ritenuto prioritario indirizzare le attività di valutazione, ed in generale l'adozione e la diffusione, delle tecnologie sanitarie in coerenza con un modello che comprenda i criteri di appropriatezza e sostenibilità degli interventi sanitari innovativi (farmaco, presidio biomedico, riorganizzazione di percorso diagnostico-terapeutico-riabilitativo complessivo nel *continuum* ospedale-territorio, ecc.) come definiti nell'allegato 1 (Programma di valutazione delle tecnologie sanitarie), parte integrante del presente provvedimento;

Ritenuto di adottare una revisione del percorso di valutazione delle suddette tecnologie, così come delineata nell'allegato 2 (Processo di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie - Atto di indirizzo), parte integrante del presente provvedimento, che aggiorna quanto stabilito dalla d.g.r. n. 7/7197 del 3 dicembre 2001, al fine di procedere ad una corretta manutenzione dei Livelli Essenziali di Assistenza e di allocare adeguatamente le risorse disponibili;

Ritenuto di istituire un Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse, con compiti e funzioni definiti negli allegati 2 (Processo di Valutazione dell'Appropriatezza d'uso delle tecnologie sanitarie. Atto di indirizzo) e 5 (Nucleo di valutazione delle priorità e dei conflitti di interesse. Regole di procedura), parti integranti del presente provvedimento, quale supporto alla Direzione Generale Sanità al fine di:

- definire le priorità (graduazione di rilevanza tecnica, sicurezza, *efficacy* o efficacia nel contesto semplificato e controllato della ricerca, *effectiveness* o efficacia nel contesto complesso della pratica, impatto economico, equità, impatto sociale ed etico, impatto organizzativo) delle valutazioni tecnologiche sanitarie la cui richiesta sia stata presentata da enti accreditati erogatori di prestazioni a carico del Sistema Sanitario Regionale, società scientifiche, ordini professionali in ambito sanitario e università aventi sede in Lombardia, nonché da industrie del farmaco, delle biotecnologie e dei dispositivi biomedici e da piccole e medie imprese operanti nei medesimi settori, secondo le modalità previste dall'allegato 3, «Modulistica elettronica per proposte di valutazione di tecnologie sanitarie», parte integrante del presente provvedimento, anche ai fini della revisione dei percorsi diagnostico-terapeutici e delle tariffe delle prestazioni;
- accertare preventivamente l'eventuale esistenza di conflitti di interesse specifici degli esperti accreditati che possano essere chiamati a predisporre i rapporti di valutazione e le analisi di impatto delle tecnologie sanitarie, secondo le procedure previste dall'allegato 5 (Nucleo di valutazione delle priorità e dei conflitti di interesse. Regole di procedura), parte integrante del presente provvedimento;

Ritenuto di dare mandato alla Direzione Generale Sanità di stabilire con successivo provvedimento le modalità applicative del percorso di valutazione delle tecnologie innovative in campo sanitario, anche avvalendosi del Tavolo Tecnico Regionale per l'Appropriatezza in Medicina, istituito con Decreto del Direttore Generale Sanità n. 9900/2006, che verrà aggiornato ed integrato con lo stesso decreto e sarà chiamato a:

- validare i rapporti di valutazione e le analisi di impatto delle tecnologie sanitarie predisposti dagli esperti accreditati e realizzati secondo procedure (a distanza e con mascheramento tra gli esperti medesimi) mirate a garantire nei limiti del possibile l'espressione di pareri multipli con criteri di multidisciplinarietà e multiprofessionalità, sulla base delle documentazioni scientifiche di efficacia presentate dai soggetti abilitati a corredo delle richieste di valutazione nonché di ogni ulteriore documentazione raccolta ed elaborata dagli esperti medesimi, dal Tavolo Tecnico Regionale per l'Appropriatezza in Medicina o dalla Direzione Generale Sanità;
- supportare la Direzione Generale Sanità nella definizione, e nel successivo monitoraggio, degli obiettivi di interesse regionale della formazione continua secondo il modello lombardo di ECM-CPD per il triennio 2008-2010 limitatamente alla voce «Programma di formazione regionale sulla Valutazione delle Tecnologie Sanitarie»;
- supportare la Direzione Generale Sanità nella implementazione di regolamentazioni mirate alla diffusione, responsabile e condivisa, di tecnologie innovative e costo-efficaci in sostituzione di tecnologie meno efficaci, sicure ed efficienti;

Ritenuto inoltre di definire un elenco aggiornabile di esperti accreditati, i quali, previa esclusione di conflitti di interesse specifici secondo le procedure previste dall'allegato 5 (Nucleo di valutazione delle priorità e dei conflitti di interesse. Regole di procedura), parte integrante del presente provvedimento, saranno chiamati a produrre rapporti di valutazione ed analisi di impatto delle tecnologie sanitarie e dei processi di cura;

Ritenuto pertanto di identificare tali esperti attraverso un invito pubblico, a cui la Direzione Generale Sanità darà ampia diffusione attraverso specifici canali di comunicazione di settore, rivolto a tutti i professionisti della salute interessati ed operanti sul territorio lombardo in qualità di dipendenti o convenzionati con le AA.SS.LL. o con gli enti erogatori del Servizio Sanitario Regionale (Aziende Ospedaliere, Fondazioni, Università), i quali potranno accreditarsi per via elettronica compilando la apposita modulistica comprensiva di «Dichiarazione Pubblica di Interessi e Impegno alla Riservatezza per componenti del Tavolo Tecnico Regionale per l'Appropriatezza in Medicina e per Esperti di tecnologie sanitarie», di cui all'allegato 4A (Invito a presentare candidature in vista della costituzione di un elenco di esperti per la valutazione delle tecnologie sanitarie. Dichiarazione pubblica di interessi e impegno alla riservatezza per componenti del tavolo tecnico regionale per l'appropriatezza in medicina e per esperti), parte integrante del presente provvedimento;

Ritenuto altresì di prevedere un compenso pari a 50 C/ora lordi (IVA inclusa) da erogare agli esperti accreditati per l'attività svolta e certificata a seguito della produzione dei rapporti di valutazione e delle analisi di impatto delle tecnologie sanitarie;

Ritenuto perciò di quantificare per l'attuazione delle attività previste per l'anno 2008 l'onere complessivo di 200.000 euro (IVA inclusa) al fine di attivare il percorso di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie in Regione Lombardia da imputare al capitolo 5.1.2.2.257.5475 che presenta la necessaria disponibilità per l'esercizio 2008;

Ritenuto di dare mandato alla Direzione Generale Sanità, sentito il Tavolo Tecnico Regionale per l'Appropriatezza in Medicina, di:

- stabilire con apposito decreto le tariffe, i criteri, le regole di procedura ed il formato atteso per la realizzazione delle Valutazioni di Efficacia Comparata e delle Schede di Valutazione di Tecnologia Sanitaria da parte degli esperti accreditati e valutati rispetto alla presenza di eventuali conflitti di interesse, nonché i criteri e le regole di procedura per l'identificazione di aree (patologie, tecnologie, prodotti, processi) orfane di valutazioni e di specifico interesse per il Sistema Sanitario Regionale (*horizon scanning*);

- stabilire con apposito decreto le modalità di verifica dell'impatto sul sistema conseguente all'utilizzo delle tecnologie sanitarie diffuse in coerenza con le valutazioni comparative e le raccomandazioni di uso approvate dal Tavolo Tecnico per l'Appropriatezza in Medicina, anche tramite la valutazione delle informazioni desumibili dall'analisi degli archivi informativi specifici (elenchi di richieste di valutazione di tecnologie sanitarie; elenchi di valutazioni realizzate; elenchi di valutazioni e raccomandazioni di uso approvate), nonché dalle analisi della Banca dati Assistito e degli altri strumenti a disposizione della programmazione regionale in materia;

Ritenuto pertanto di definire il processo per la valutazione dell'appropriatezza d'uso di tecnologie innovative (farmaci, dispositivi biomedici, tecnologie diagnostico-terapeutiche, adattamenti dei percorsi diagnostico-terapeutico-riabilitativi ed assistenziali) al fine del loro ottimale impiego nell'ambito del Servizio Sanitario Regionale e di approvare a tal fine i seguenti allegati, parti integranti e sostanziali del presente provvedimento:

- Allegato 1 «Programma di valutazione delle Tecnologie Sanitarie»;
- Allegato 2 «Processo di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie – Atto di indirizzo»;
- Allegato 3 «Schema Tipo di modulistica elettronica per proposte di valutazione di tecnologie sanitarie»;
- Allegato 4A «Invito a presentare candidature in vista della costituzione di un elenco di esperti per la valutazione delle tecnologie sanitarie. Dichiarazione pubblica di interessi e impegno alla riservatezza per componenti del tavolo tecnico regionale per l'appropriatezza in medicina e per esperti»;
- Allegato 4B «Valutazione delle Tecnologie Sanitarie. Dichiarazione pubblica di interessi e impegno alla riservatezza per componenti del tavolo tecnico regionale per l'appropriatezza in medicina e per esperti»;
- Allegato 5 «Nucleo di Valutazione delle Priorità e dei Conflitti di Interessi (NVPCI). Regole di procedura»;

Stabilito che la Direzione Generale Sanità potrà attivare specifici accordi convenzionali con le Strutture Sanitarie Lombarde, a supporto delle azioni previste dal presente programma di valutazione di tecnologie sanitarie;

Ritenuto infine di:

- dare mandato alla Direzione Generale Sanità di assumere le ulteriori determinazioni necessarie alla piena attuazione del presente provvedimento;
- di pubblicare il presente provvedimento sul Bollettino Ufficiale della Regione Lombardia e sul sito internet della Direzione Generale Sanità;

Vista la legge regionale 11 luglio 1997, n. 31 «Norme per il riordino del Servizio Sanitario Regionale e sua integrazione con le attività dei servizi sociali» e successive modifiche;

Vagliate e fatte proprie le suddette motivazioni

All'unanimità dei voti espressi ai sensi di legge;

DELIBERA

1. di definire il processo per la valutazione dell'appropriatezza d'uso di tecnologie innovative al fine del loro ottimale impiego nell'ambito del Servizio Sanitario Regionale e di approvare a tal fine i seguenti allegati, parti integranti del presente provvedimento:

- Allegato 1 «Programma di valutazione delle Tecnologie Sanitarie»;
- Allegato 2 «Processo di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie – Atto di indirizzo»;
- Allegato 3 «Schema Tipo di modulistica elettronica per proposte di valutazione di tecnologie sanitarie»;
- Allegato 4A «Invito a presentare candidature in vista della costituzione di un elenco di esperti per la valutazione delle tecnologie sanitarie. Dichiarazione pubblica di interessi e impegno alla riservatezza per componenti del tavolo tecnico regionale per l'appropriatezza in medicina e per esperti»;
- Allegato 4B «Valutazione delle Tecnologie Sanitarie. Dichiarazione pubblica di interessi e impegno alla riservatezza per componenti del tavolo tecnico regionale per l'appropriatezza in medicina e per esperti»;

- Allegato 5 «Nucleo di Valutazione delle Priorità e dei Conflitti di Interessi (NVPCI). Regole di procedura»;
- 2. di stabilire un compenso pari a 50 euro/ora lordi (IVA inclusa) agli esperti accreditati per l'attività svolta e certificata a seguito della produzione dei rapporti di valutazione e delle analisi di impatto delle tecnologie sanitarie;
- 3. di quantificare per l'attuazione delle attività previste per l'anno 2008 l'onere complessivo di 200.000 euro (IVA inclusa) al fine di attivare il percorso di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie in Regione Lombardia da imputare al capitolo 5.1.2.2.257.5475 che presenta la necessaria disponibilità per l'esercizio 2008;
- 4. di precisare che a decorrere dall'anno 2008 il contributo per gli obiettivi PSSR riconosciuto alle aziende pubbliche deve tenere obbligatoriamente conto della reale produzione delle attività di ricovero e di specialistica a contratto;
- 5. di dare mandato alla Direzione Generale Sanità di assumere le ulteriori determinazioni necessarie alla piena attuazione del presente provvedimento;
- 6. di pubblicare il presente provvedimento sul Bollettino Ufficiale della Regione Lombardia e sul sito internet della Direzione Generale Sanità.

Il segretario: Pilloni

_____ • _____

PROGRAMMA DI VALUTAZIONE DELLE TECNOLOGIE SANITARIE

1.1 Introduzione

Il Piano Socio Sanitario 2007-2009 individua la valutazione delle tecnologie in termini di efficacia e di costi come priorità di un programma di eccellenza e definisce «*Health technology*» come «... un'espressione con cui, a livello internazionale, per convenzione, si intende ogni metodo utilizzato per promuovere la salute, prevenire e trattare una malattia, migliorare la riabilitazione o definire criteri di cura e assistenza a lungo termine. In questo contesto, le tecnologie non sono soltanto i nuovi farmaci o le apparecchiature sofisticate, ma anche le procedure, le modalità di assistenza ed i programmi di screening. In altri termini, nel linguaggio della HTA, *health technology* copre ogni metodo usato da coloro che lavorano nei servizi sanitari per promuovere la salute, prevenire e trattare una malattia o una specifica condizione clinica, migliorare la riabilitazione e l'assistenza a lungo termine» (1).

La valutazione delle tecnologie sanitarie (*Health Technology Assessment*, HTA) si configura quindi come un processo di gestione delle conoscenze (*knowledge management*) sanitarie operato a tutti i livelli del SSR e che prende in esame varie dimensioni di impatto delle tecnologie sanitarie e ne compara benefici e costi. Comprende almeno tre macroprocessi (2):

- a) identificazione delle priorità per il sistema sanitario e delle necessità di valutazione per il sistema sanitario;
- b) reperimento sistematico ed analisi coerente delle documentazioni di efficacia disponibili (o identificazione esplicita della carenza di documentazione);
- c) valutazione critica delle documentazioni di efficacia, comprensiva del giudizio circa il significato pratico (applicazione) nella prospettiva del sistema sanitario.

Obiettivo generale del programma regionale lombardo di valutazione delle tecnologie sanitarie è facilitare la diffusione nella pratica clinica delle tecnologie più efficaci, sicure ed efficienti in sostituzione/alternativa di tecnologie meno efficaci, sicure ed efficienti, secondo modalità condivise, trasparenti, monitorabili e verificabili e che attribuiscono chiare responsabilità ai soggetti coinvolti.

Obiettivi specifici del processo di valutazione sono i seguenti:

- 1) gestire il livello di incertezza (talvolta ineliminabile) delle informazioni sulle tecnologie sanitarie;
- 2) gestire la trasferibilità nel sistema sanitario regionale delle valutazioni (compresi i risultati della ricerca) prodotte in altri contesti, nazionali ed internazionali;
- 3) sperimentare approcci innovativi nell'uso pratico di biotecnologie, biomedicine, biosimilari ed in generale prodotti e processi d'avanguardia;
- 4) gestire le questioni elencate ai tre punti precedenti all'interno di un modello decisionale orientato alla sostenibilità economica e all'appropriatezza specifica.

Il prodotto atteso dal processo regionale di valutazione dell'appropriatezza d'uso di farmaci, dispositivi biomedici e tecnologie diagnostico-terapeutiche consiste in un insieme coerente di sintesi informative di alta qualità e credibilità, fruibile da parte di diversi attori del sistema sanitario distribuiti ai diversi livelli di assistenza, anche quale contributo per il programma Mappa della Medicina di Regione Lombardia.

1.2 Modello

Le valenze clinico-sanitarie e sociali sottese al programma di valutazione delle tecnologie in sanità si inquadrano all'interno di un riferimento economico caratterizzato da una situazione di *competizione* per l'uso delle risorse (indipendentemente dal livello di finanziamento disponibile, le risorse saranno sempre insufficienti a sostenere tutte le attività auspicabili) che richiede l'uso di tre principi:

- scelta (poiché le risorse non sono illimitate, occorre scegliere tra modi differenti di usarle);
- costo/opportunità (una scelta di impiego di risorse in una direzione determinata implica il mancato impiego delle stesse risorse in altre direzioni, e quindi la perdita di opportunità alternative);
- analisi dei costi e dei benefici marginali (3).

All'interno di questo contesto, non solo la quantità minima di risorse dovrebbe essere usata per ottenere un risultato pari o migliore in termini di efficacia (efficienza tecnica), ma dovrebbe essere tenuto in debito conto il possibile miglior uso alternativo delle stesse risorse (costo-opportunità). In particolare, è il rapporto costo-efficacia incrementale (ICER, *Incremental Cost-Effectiveness Ratio*) ad essere usato quale metodo standard nelle analisi costo-efficacia. Viene calcolato dividendo la differenza tra i costi (della tecnologia innovativa e di quella tradizionale) per la differenza tra gli effetti, in modo da ottenere il costo addizionale per unità di esito (*outcome*) addizionale.

Peraltro le analisi di costo-efficacia, che pur costituiscono validi strumenti di supporto alle decisioni allocative, non devono assumere la forma di regole decisionali rigide e incontrovertibili; le priorità infatti devono sempre essere riviste alla luce di emergenze sociali o di altro tipo.

In genere il sostegno ad un processo decisionale in materia di allocazione delle risorse viene meno laddove viene data prevalenza al raggiungimento di una maggiore o pari efficacia del trattamento rispetto al miglioramento dell'efficienza tecnica. Ossia, un valore positivo di ICER significa che le risorse attualmente impiegate per l'intervento tradizionale non sarebbero sufficienti a coprire i costi dell'intervento innovativo qualora questo venisse applicato al medesimo numero di pazienti finora trattato con l'intervento tradizionale. Un valore positivo di ICER espone quindi a questioni di equità di accesso di non facile soluzione.

In letteratura questo aspetto sembra essere sottovalutato (4), finendo per propagandare la validità di situazioni in cui

(1) Si veda anche la definizione di tecnologia sanitaria di European network for Health Technology Assessment, disponibile presso: <http://www.eunethta.eu/HTA/> (consultato il 2 gennaio 2008).

(2) Health Technologies and Decision Making – OECD 2005.

(3) Mitton C, Donaldson C.: Come stabilire le priorità in sanità. Una guida all'applicazione dell'economia nel processo decisionale. Il Pensiero Scientifico Editore, 2006.

(4) Cfr. Donaldson C., Currie G., Mitton C.: Cost effectiveness analysis in health care: contraindications. *BMJ* 2002; 325: 891-4.

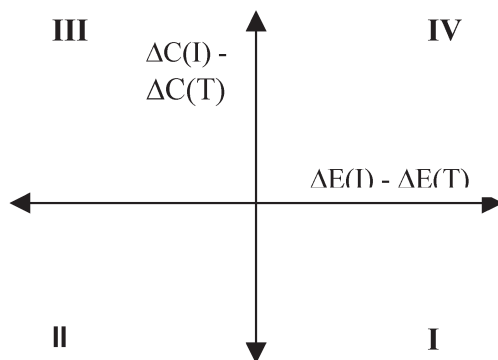
migliori risultati vengono ottenuti solo in seguito ad un incremento dei costi, e mettendo in ombra l'impatto sull'allocazione delle risorse (efficienza allocativa) e sul relativo costo-opportunità, che mantiene, invece, un ruolo decisivo nella pratica programmatoria della sanità.

Infine, le analisi di costo-efficacia richiedono correzioni statistiche appropriate al fine di tener conto dell'incertezza delle assunzioni adottate riguardo ai costi e ai benefici. Analisi di sensitività univariate e multivariate, stima degli intervalli di confidenza, benefici netti di salute (*Net Health Benefits*, NBH) con valori soglia di costo-efficacia, curve di accettabilità di costo-efficacia sono alcuni dei metodi suggeriti a questo scopo, ma non consentono di risolvere il problema della intrinseca soggettività della scelta dei valori soglia.

In sintesi il rapporto ICER non prende adeguatamente in considerazione i due principi sopra richiamati, in particolare il costo/opportunità, e necessita quindi di essere interpretato ed integrato.

Un approccio alternativo consiste nell'identificazione di miglioramenti di salute non ambigui effettivamente ottenibili con le risorse disponibili. In questo caso i benefici di salute incrementali che si stima siano raggiungibili con l'applicazione delle strategie innovative sono comparati con i benefici di salute attualmente ottenuti con quella combinazione di strategie tradizionali che è necessario dismettere al fine di generare sufficienti risorse per finanziare le strategie innovative (5). Quando, e solo quando, i benefici di salute incrementali delle strategie innovative eccedono i benefici di salute attuali delle strategie tradizionali si identifica una occasione di miglioramento dell'efficienza allocativa. In caso opposto, il programma proposto come innovativo non è verificato come tale e viene pertanto posto ad un livello di priorità minore.

Il modello costo-efficacia così integrato è rappresentabile con l'uso del seguente diagramma decisionale, costituito da quattro quadranti delimitati dalla differenza tra i benefici (o effetti) dei programmi innovativo e tradizionale (asse orizzontale) e della differenza tra i costi dei programmi innovativo e tradizionale (asse verticale) (6).



Ove:

- $DC(I)$ = costo incrementale del (o risorse aggiuntive necessarie per il) programma innovativo (I) rispetto al costo di trattamento del medesimo numero di pazienti in assenza del programma (I)
- $DC(T)$ = risparmio incrementale (o risorse liberate) ottenibile dalla cancellazione del programma tradizionale (T), ovvero costo del programma (T) rispetto al costo di trattamento del medesimo numero di pazienti in assenza del programma (T)
- $DE(I)$ = beneficio incrementale ottenibile con l'impiego del programma (I) rispetto al beneficio garantito al medesimo numero di pazienti in assenza del programma (I)
- $DE(T)$ = beneficio decrementale associato alla cancellazione del programma (T), rispetto al beneficio garantito al medesimo numero di pazienti in assenza del programma (T).

Per ogni proposta di intervento innovativo può essere quindi calcolato un valore medio teorico (definibile, a fini pratici, quale costo-opportunità incrementale bilanciato) e tale valore può essere rappresentato sul diagramma decisionale per effettuare valutazioni comparative tra molteplici interventi.

L'incertezza degli assunti di base (riguardo cioè ai parametri che compongono i benefici ed i costi) può essere stimata considerando benefici e costi come parametri stocastici ed applicando un approccio bayesiano. La stima delle probabilità così calcolate può quindi essere rappresentata come distribuzione congiunta costo-beneficio all'interno del diagramma decisionale.

Il quadrante I identifica una maggiore efficienza allocativa delle risorse: in questo caso la sostituzione del programma tradizionale (T) con il programma innovativo (I) si traduce in un guadagno netto di salute senza la necessità di risorse aggiuntive.

Il quadrante II identifica casi di risparmio di risorse accompagnato peraltro da riduzione netta di salute e quindi casi non auspicabili.

Il quadrante III rappresenta situazioni di aumento dei costi e concomitante diminuzione dei benefici di salute, e identifica quindi la peggiore efficienza allocativa.

Il quadrante IV rappresenta infine casi di concomitante aumento dei costi e dei benefici. La maggior parte delle tecnologie la cui innovatività è documentata da un ICER positivo ricade in questo quadrante.

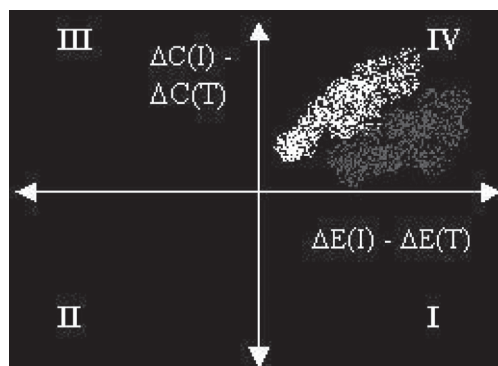
Le valutazioni la cui distribuzione della stima dei risultati ricada nel quadrante I (compresi gli assi verticale ed orizzontale con l'esclusione dell'origine) soddisfano l'algoritmo di miglioramento dell'efficienza allocativa ed identificano quindi tecnologie che meriterebbero una rapida applicazione su vasta scala.

Le valutazioni la cui distribuzione della stima dei risultati ricada nei quadranti II o III non soddisfano l'algoritmo di miglioramento dell'efficienza allocativa e identificano quindi tecnologie che devono essere evacuate dal sistema alla maggiore

(5) Gafni A, Birch S CMAJ 2003; 168(7).

(6) Senti P, Gafni A, Birch S.: Opportunity costs and uncertainty in the economic evaluation of health care interventions. Health Econ 2002; 11: 23-31.

velocità e scala possibile (nel caso del quadrante **III**, anche per la possibile documentazione di perdite nette di benefici, in termine di salute).



Distribuzione della stima dei risultati ottenibili dalla sostituzione della tecnologia tradizionale (punti in nero) con la tecnologia innovativa (punti in grigio chiaro).

Le valutazioni la cui distribuzione della stima dei risultati ricada nel quadrante **IV** soddisfano solo parzialmente l'algoritmo dell'efficienza allocativa. In questo caso è comunque possibile identificare dei miglioramenti dell'efficienza allocativa almeno in termini relativi. Come illustrato nella figura, una valutazione la cui distribuzione della stima dei risultati dell'intervento innovativo (punti in grigio chiaro) pur ricadendo nel quadrante **IV** si situi in un'area più in basso e a destra rispetto alla distribuzione dei risultati dell'intervento tradizionale (punti in nero) renderebbe esplicito il vantaggio della sostituzione, nella misura in cui le distribuzioni non si sovrappongono significativamente.

Il diagramma decisionale consente quindi di rendere espliciti i benefici attesi dall'implementazione (o dalla mancata implementazione) di programmi innovativi (I) in sostituzione di (e non in aggiunta a) programmi tradizionali (T). Consente inoltre di indirizzare il mercato verso la identificazione e lo sviluppo di aree di opportunità sostenibili e socialmente credibili, ad esempio la progettazione e realizzazione di tecnologie che si posizionino nella parte bassa e a destra del quadrante IV ovvero nel quadrante I, rispetto a tecnologie esistenti posizionate in altri quadranti.

L'adozione dell'approccio valutativo che interpreta le valutazioni di costo-efficacia entro un quadro comparativo che considera gli elementi di costo/opportunità, corretto per l'incertezza negli assunti di costo e di beneficio ove necessario e rappresentato con l'ausilio del diagramma decisionale, consente quindi di identificare e documentare le tecnologie (farmaci, protesica, altre tecnologie) più efficaci, sicure ed efficienti in sostituzione/alternativa di tecnologie meno efficaci, meno sicure ed efficienti, secondo modalità:

- *responsabili*, perché indirizza i partner industriali e il mondo della ricerca e della clinica verso la costruzione di standard credibili fin dalla presentazione delle proposte di ricerca o valutazione tecnologica;
- *condivise*, perché facilita il coinvolgimento di tutti i portatori di interesse nella valutazione dei pro e contro inerenti ad ogni decisione allocativa;
- *trasparenti*, perché aumenta il livello di documentazione esplicita del processo di valutazione delle tecnologie;
- *monitorabili*, perché la diffusione delle tecnologie è tracciabile fin dalla fase della loro introduzione grazie alla esplicita definizione di indicatori previsionali d'utilizzo;
- *verificabili*, perché il livello di utilizzo effettivo può essere confrontato con il livello standard predeterminato e dar luogo quindi ad interventi correttivi qualora i risultati osservati non siano conformi a quelli attesi;
- economicamente *sostenibili*, nella prospettiva del terzo pagante ma anche del cittadino-cliente;
- *accessibili alla libera concorrenza*, nella prospettiva del produttore e del venditore.

1.3 Implementazione

Poiché è documentata la scarsa efficacia, ai fini dell'adozione di pratiche più costo/efficaci e dismissione di pratiche meno costo/efficaci, della semplice disseminazione o disponibilità *just in time* di informazioni, il processo di produzione e disseminazione delle sintesi informative (valutazioni comparative dell'appropriatezza di uso) necessita di un raccordo con:

- iniziative di formazione specifica nell'ambito del sistema di Sviluppo Professionale Continuo ECM-CPD;
- strumenti informativi sanitari a livello regionale (SISS) ed aziendale (aree intranet delle ASL, AO, Fondazioni);
- strumenti gestionali sanitari a livello regionale ed aziendale (Accordi di Governo Clinico e altri strumenti).

L'adozione graduale di iniziative coordinate negli ambiti informativo, formativo e gestionale può infatti consentire quello sviluppo culturale, orientato alla documentazione non solo dell'efficacia pratica (*effectiveness*) ma anche del rapporto costo/efficacia, che è determinante per il miglioramento progressivo dalla qualità e dell'appropriatezza specifica in sanità.

Al fine di facilitare il progressivo raccordo tra le anzidette infrastrutture e gestioni, si identificano i seguenti indirizzi:

1.3.a) Iniziative di formazione:

- gli obiettivi di interesse regionale della formazione continua secondo il modello lombardo di ECM-CPD potranno essere integrati, a titolo sperimentale per l'anno 2009, con la voce «Programma di formazione regionale sulla Valutazione delle Tecnologie Sanitarie»;
- la partecipazione attiva al Programma di formazione regionale di Valutazione delle Tecnologie Sanitarie è considerata elemento qualificante del portfolio summativo-formativo del professionista sanitario appartenente al Sistema Sanitario Regionale, si sostanzia in un contributo individuale al processo regionale di elaborazione di Valutazioni di Efficacia

Comparata o di Schede di Valutazione di Tecnologia Sanitaria (predisposte secondo gli indirizzi riportati nell'allegato 6 del presente provvedimento) e contribuisce ad assolvere al debito formativo per la quota associata agli obiettivi di interesse regionale;

- il processo regionale di elaborazione di Schede di Valutazione di Tecnologia Sanitaria richiede l'espletamento coordinato e finalizzato di «ricerca ed organizzazione di documentazione, lettura di testi e/o di articoli scientifici, confronti tra soluzioni in gruppo opportunamente guidato, analisi di casi e situazioni, redazione, presentazione e discussione di relazioni e documenti». Tali attività di norma necessitano di interazione a distanza (nel tempo e nello spazio) e sono quindi qualificate come interventi di Formazione sul Campo in forma Integrata (in presenza e a distanza), tipologia «Partecipazione a gruppi di miglioramento» come da d.g.r. 5961 del 5 giugno 2007 «Educazione Continua in Medicina – Sviluppo Professionale Continuo (ECM-CPD): indicazioni operative per la progettazione di interventi di Formazione sul Campo (FsC) in coerenza con il modello lombardo»;
- con successivo provvedimento della Direzione Generale Sanità potrà essere demandato alle ASL, AO e Fondazioni l'inserimento, nel Piano di Formazione Aziendale per l'anno 2009, di una voce di progetto denotata «Formazione continua sulla Valutazione delle Tecnologie Sanitarie», nonché la registrazione delle attività in presenza realizzate dal professionista quale contributo individuale al processo di elaborazione di Schede di Valutazione di Tecnologia Sanitaria;
- le ASL, le AO e le Fondazioni collaborano con l'Istituto Regionale della Formazione (IReF) al fine di assicurare l'accreditamento dei partecipanti al «Programma di formazione regionale sulla Valutazione delle Tecnologie Sanitarie».

1.3.b) Strumenti informativi:

- le Valutazioni di Efficacia Comparata e le Schede di Valutazione di Tecnologia Sanitaria costituiranno un contributo per l'aggiornamento dinamico dei contenuti della Mappa della Medicina on-line di Regione Lombardia, il cui prototipo, previsto per l'anno 2008 presso alcune ASL pilota, verrà successivamente disseminato sul territorio regionale previo coinvolgimento delle ASL, AO e Fondazioni.

1.3.c) Strumenti gestionali:

- le Valutazioni di Efficacia Comparata e le Schede di Valutazione di Tecnologia Sanitaria costituiranno specifico contributo informativo di riferimento (cfr. Allegato 5: Farmaceutica e Protesica – d.g.r. n. 8/5743 del 31 ottobre 2007 per le seguenti questioni:
 - valutazione, da parte delle ASL, del mix di prescrizioni appropriate per l'iter diagnostico-terapeutico di riferimento;
 - promozione di Percorsi Diagnostico-Terapeutici condivisi tra ASL e AO per uso appropriato di farmaci in patologie croniche ad alto costo (esempio BPCO, HIV, artrite reumatoide, ecc.);
 - condivisione tra AO/Fondazioni e ASL di prontuari alla dimissione, in cui saranno valutate le iniziative aziendali tese a diffondere tra gli operatori sanitari (clinici e farmacisti) l'uso e la prescrizione alla dimissione dei farmaci equivalenti (in particolare ATC: A02, C10, C09, C08, N06, J01);
 - promozione di iniziative di informazione e di formazione specifica per i medici prescrittori del territorio e delle strutture ospedaliere relativamente ai farmaci di maggiore utilizzo e finalizzate alla appropriatezza prescrittiva intesa come corretto dosaggio di farmaco prescritto e continuità temporale di adesione alla terapia (cosiddetta persistenza) dei pazienti;
- le Valutazioni di Efficacia Comparata e le Schede di Valutazione di Tecnologia Sanitaria costituiranno inoltre contributo informativo per le attività di contrattazione decentrata e di determinazione aziendale degli Accordi di Governo Clinico per la Medicina Generale e la Pediatria di libera scelta;
- le Valutazioni di Efficacia Comparata e le Schede di Valutazione di Tecnologia Sanitaria costituiranno inoltre contributo informativo per le attività aziendali previste da parte dei Collegi di Direzione e dei Consigli dei Sanitari delle AA.OO. e delle Fondazioni, nonché per le attività previste da parte degli organismi gestionali dei Piani di settore e di Sviluppo (Oncologico, Cerebrocardiovascolare, ecc.) di cui all'allegato 6 della d.g.r. n. 8/5743 del 31 ottobre 2007.

PROCESSO DI VALUTAZIONE DELL'APPROPRIATEZZA D'USO DELLE TECNOLOGIE SANITARIE ATTO DI INDIRIZZO

Il presente documento definisce e pone in relazione gli elementi costitutivi del processo di valutazione dell'appropriato uso delle tecnologie in ambito sanitario previsto all'interno del Sistema Sanitario Regionale.

AMBITO DI APPLICAZIONE

Il processo di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie si applica a numerosi processi e prodotti previsti nei Livelli Essenziali di Assistenza, quali:

- farmaci e dispositivi biomedici, compresi i prodotti bioequivalenti o biosimilari ed i derivati nanotecnologici (dotati di Autorizzazione all'Immissione in Commercio – AIC – o di marchio CE);
- tecnologie diagnostico-terapeutiche di natura non farmacologica;
- revisioni (anche in forma di *audit* clinico ed organizzativo) ed innovazioni di procedure e percorsi preventivi (screening), diagnostico-terapeutici, riabilitativi;
- sistemi organizzativi e di supporto coordinati (amministrativi, formativi, informativi) che predispongono, abilitano o rinforzano l'uso appropriato delle tecnologie sanitarie;
- l'interrelazione tra i precedenti fattori

ed indirizza, coordina e supporta le decisioni allocative (tariffe e rimborsi), applicative (frequenza e intensità di uso) e valutative (monitoraggio, dismissione e sostituzione) delle tecnologie sanitarie.

Dal presente processo di valutazione dell'appropriatezza d'uso delle tecnologie sanitarie è specificamente esclusa la ricerca di base e le attività di esclusiva sperimentazione pre-clinica e clinica.

FASI DEL PROCESSO

Sono almeno tre, sequenziali e cicliche: l'identificazione dei bisogni di valutazione, la raccolta e l'interpretazione delle documentazioni pertinenti e l'esame dei risultati finalizzato all'assunzione di decisioni allocative ed applicative. Tali decisioni necessitano di monitoraggi periodici e predeterminati che possono condurre a revisioni o a conferme delle decisioni assunte.

Ogni fase è caratterizzata da attività intercorrelate che possono evolvere anche tramite iterazioni successive in sottoprodotti intermedi o finali.

ELENCO DELLE ATTIVITÀ PREVISTE

Fase A – Identificazione delle necessità di valutazione e delle priorità per il sistema sanitario

ATTORI DEL PROCESSO:

- Regione Lombardia
 - Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse (NVPCI)
 - soggetti accreditabili.
1. Raccolta e validazione delle richieste di valutazione avanzate da soggetti accreditati
 2. Identificazione delle ulteriori necessità di valutazione non avanzate da soggetti accreditati (aree «orfane di valutazione»)
 3. Catalogazione delle richieste di valutazione (e delle necessità di valutazione in aree orfane) secondo una graduazione di priorità multidimensionale su scala ordinale e livelli predefiniti (da 1 = valore minimo a 5 = valore massimo) per ognuna delle seguenti otto dimensioni **(1)**:
 - Rilevanza tecnica in termini comparativi rispetto a standard *de facto* o formali
 - Sicurezza in termini comparativi rispetto a standard *de facto* o formali
 - Efficacia nel contesto di ricerca clinica (studi clinici; *efficacy*) in termini comparativi rispetto a standard *de facto* o formali
 - Efficacia nel contesto della medicina pratica (ad es. giudizio di generalizzabilità o validità esterna per gli studi clinici; *effectiveness*) in termini comparativi rispetto a standard *de facto* o formali, con particolare attenzione a patologie croniche e sottopopolazioni complesse e con alti livelli di comorbidità
 - Impatto economico e finanziario in termini comparativi rispetto a standard *de facto* o formali (ad esempio analisi di costo-efficacia e esplicita identificazione di tecnologie di cui si propone la sostituzione o la riduzione controllata di utilizzo)
 - Equità in termini comparativi rispetto a standard *de facto* o formali (ad esempio impatto sull'accesso al mix di tecnologie diagnostico-terapeutiche generato dall'adozione di una tecnologia innovativa)
 - Impatto sociale ed etico rispetto a standard *de facto* o formali (ad esempio analisi qualitative di gradimento e accettabilità ovvero implicazioni non immediatamente evidenti che derivano dall'uso delle tecnologie)
 - Impatto organizzativo rispetto a standard *de facto* o formali (ad esempio fattori collegati all'implementazione e al mantenimento in uso delle tecnologie)
 4. Calcolo di un punteggio globale di priorità
 5. Attribuzione di un stima di incertezza ad ognuna delle precedenti dimensioni
 6. Rappresentazione delle priorità e delle incertezze tramite grafici cumulativi «a radar» per aree patologiche o settori sanitari, al fine di evidenziare aree orfane o aree comunque meritevoli di ulteriori approfondimenti.

Sottoprodotto intermedio atteso: database di richieste espresse (ed inesprese) di valutazione di tecnologie sanitarie.

(1) Hailey D: Toward transparency in Health Technology Assessment – A Checklist for HTA Reports. Int J Tech Ass in Health Care 2003; 19(1): 1-7.

Fase B – Reperimento sistematico ed analisi coerente delle documentazioni di efficacia disponibili (o identificazione della carenza di documentazione)

ATTORI DEL PROCESSO:

- soggetti accreditabili
- Nucleo di Valutazione dei Conflitti di Interesse, esperti accreditati
- Regione Lombardia, Tavolo Tecnico per l'Appropriatezza in Medicina.
- 7. Raccolta delle documentazioni scientifiche e delle osservazioni pratiche (ad es. analisi secondaria dei database amministrativi) concernenti tecnologie sanitarie, estesa ad ognuna delle dimensioni oggetto della determinazione di priorità (rilevanza tecnica, sicurezza, *efficacy*, *effectiveness*, impatto economico, equità, impatto sociale ed etico, impatto organizzativo)
- 8. Sintesi dei dati principali desumibili dalle documentazioni scientifiche e dalle osservazioni pratiche, secondo un formato predefinito
- 9. Committenza di valutazioni specifiche ad esperti accreditati e valutati riguardo al possibile conflitto di interessi specifico in atto o potenziale
- 10. Interpretazione, rispetto a standard *de facto* o formali, delle documentazioni scientifiche e delle osservazioni pratiche concernenti tecnologie sanitarie da parte degli esperti accreditati e valutati riguardo al rispettivo conflitto di interesse. Tale interpretazione viene articolata per ognuna delle otto dimensioni oggetto della determinazione di priorità
- 11. Sintesi e consolidamento di valutazioni specifiche comparative rispetto a standard *de facto* o formali, redatte secondo formati prestabiliti

Sottoprodotto intermedio atteso: database di valutazioni specifiche comparative collegate alle documentazioni rilevanti e interpretate secondo criteri di priorità multidimensionali.

Fase C – Valutazione critica delle documentazioni di efficacia, comprensiva del giudizio circa il significato pratico (applicazione) nella prospettiva del sistema sanitario.

ATTORI DEL PROCESSO:

- Regione Lombardia
- Tavolo Tecnico per l'Appropriatezza in Medicina
- esperti accreditati.
- 12. Esame delle valutazioni comparative secondo la prospettiva del servizio sanitario regionale e formulazione delle raccomandazioni di uso
- 13. Disseminazione dei risultati e delle raccomandazioni di uso secondo strategie multiple e coordinate (formative, informative, gestionali)
- 14. Controllo dell'impatto ottenuto dalle raccomandazioni di uso delle tecnologie sanitarie.

Sottoprodotto finale atteso: database di raccomandazioni di uso di tecnologie sanitarie specifiche, aggiornato e validato a livello regionale, finalizzato ad informare le decisioni allocative (tariffe di rimborso), le decisioni applicative (intensità e frequenza di prescrizione ed impiego) e le decisioni valutative (ad es. audit clinici, o controlli esterni, di appropriatezza specifica per percorso diagnostico-terapeutico complessivo).

DESCRIZIONE ANALITICA DELLE ATTIVITÀ PREVISTE

Fase A – Identificazione delle necessità di valutazione e delle priorità per il sistema sanitario

1. Raccolta e validazione delle richieste di valutazione avanzate da soggetti accreditati

I soggetti accreditabili ai fini della presentazione di richieste di valutazione di tecnologie sanitarie sono classificati in due categorie:

- Enti non lucrativi o *no profit* (organizzazioni i cui avanzi di gestione utili sono interamente reinvestiti per gli scopi organizzativi):
 - enti accreditati erogatori di prestazioni a carico del Sistema Sanitario Regionale;
 - società scientifiche a carattere sanitario aventi sede in Lombardia;
 - ordini professionali in ambito sanitario aventi sede in Lombardia;
 - associazioni di pazienti aventi sede in Lombardia;
 - università lombarde.
- Enti lucrativi:
 - industrie del farmaco delle biotecnologie e dei dispositivi biomedici;
 - industrie operanti nella diagnostica;
 - piccole e medie imprese operanti nei settori del farmaco, delle biotecnologie, dei dispositivi biomedici e della diagnostica.

Le richieste di valutazione di tecnologie sanitarie vengono avanzate esclusivamente per via elettronica tramite apposito sistema informativo predisposto con successivo provvedimento della Direzione Generale Sanità e comprendente la compilazione di modulistica elettronica il cui tracciato è definito nell'allegato 3. La presentazione di una richiesta di valutazione di tecnologie sanitarie è seguita, nel caso di ammissione alla valutazione, dal versamento di una tariffa quale compartecipazione alla copertura dei costi del processo di valutazione. Il valore della tariffa (che sarà definito con successivo atto della Direzione Generale Sanità) è differenziato secondo la tipologia generale di tecnologia proposta e secondo la natura dei soggetti accreditabili:

- valore nominale per le richieste presentate da parte di enti non lucrativi;
 - valore effettivo per le richieste presentate da parte di enti lucrativi.
- Le richieste di valutazione non accompagnate da documentazione completa o dal versamento della tariffa prevista non saranno validate dalla Direzione Generale Sanità e saranno archiviate in apposito elenco di richieste incomplete. Di tale archiviazione verrà data notizia agli enti interessati.
- Le richieste di valutazione completate saranno inoltrate al Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse ai fini della catalogazione e dell'emissione del giudizio di priorità (cfr. successivo punto 3).
- L'accesso all'intero sistema informativo delle richieste di valutazione tecnologica sanitaria è riservato ai componenti del Tavolo Tecnico per l'Appropriatezza in Medicina e ai componenti del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse, oltre che ai funzionari alla Direzione Generale Sanità.
- L'accesso alla documentazione informatica pertinente alle singole valutazioni è riservato agli esperti accreditati e identificati dopo il completamento della rispettiva procedura di valutazione dei conflitti di interesse di cui all'allegato 5.

2. Identificazione delle ulteriori necessità di valutazione non avanzate da soggetti accreditati (aree «orfane di valutazione»)

L'*horizon scanning* ed in generale l'identificazione di aree (patologie, tecnologie, prodotti, processi) meritevoli di valutazioni di specifico interesse per la sanità pubblica sono demandate ad un successivo provvedimento della Direzione Generale Sanità e previa verifica tecnica della fattibilità da parte del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse.

3. Catalogazione delle richieste di valutazione (e delle necessità di valutazione in aree orfane)

- La Direzione Generale Sanità predispone all'ordine del giorno delle riunioni del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse l'elenco delle richieste di valutazione tecnologica sanitaria e ne fornisce le indicazioni di accesso alla documentazione completa, esclusivamente per via elettronica, entro 1 mese dalla data di convocazione del Nucleo.
- Durante le riunioni del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse le richieste di valutazione vengono presentate brevemente (20' massimo) da parte di un funzionario della Direzione Generale Sanità con il supporto della documentazione fornita a corredo della richiesta di valutazione tecnologica (già inserita per via elettronica da parte dell'ente richiedente ed eventualmente integrata).
- I componenti del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse effettuano un giudizio personale ed indipendente di priorità ai fini dell'ammissibilità alla valutazione, avvalendosi di schede opportunamente predisposte.
- La graduazione di priorità è effettuata utilizzando una griglia multidimensionale su scala ordinale con livelli predefiniti (da 1 = valore minimo a 5 = valore massimo) per ognuna delle otto dimensioni sotto riportate.
- I livelli soglia ai fini della ammissione alla valutazione vengono stabiliti dai componenti del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse in occasione della riunione di insediamento e successive.

Dimensioni del giudizio di ammissione alla valutazione e di priorità

3.1. Rilevanza tecnica in termini comparativi rispetto a standard *de facto* o formali

Stima di rilevanza tecnica	1	2	3	4	5
	Minima	F			Massima
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di rilevanza tecnica della proposta innovativa					

3.2. Sicurezza in termini comparativi rispetto a standard *de facto* o formali

Stima di sicurezza	1	2	3	4	5
	Minima	F			Massima
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di sicurezza della proposta innovativa					

3.3. Efficacia nel contesto di ricerca (studi clinici; *efficacy*) in termini comparativi rispetto a standard *de facto* o formali

Stima di efficacia nel contesto di ricerca clinica (<i>efficacy</i>)	1	2	3	4	5
	Minima	F			Massima
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di efficacia, nel contesto di ricerca clinica, della proposta innovativa					

3.4. Efficacia nel contesto della medicina pratica (ad es. giudizio di generalizzabilità o validità esterna per gli studi clinici; *effectiveness*) in termini comparativi rispetto a standard *de facto* o formali, con particolare attenzione a patologie croniche e sottopopolazioni complesse e con alti livelli di comorbidità

Stima di efficacia nel contesto della medicina pratica (<i>effectiveness</i>)	1	2	3	4	5
	Minima	F			Massima
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di efficacia, nel contesto della medicina pratica, della proposta innovativa					

3.5. Impatto economico in termini comparativi rispetto a standard *de facto* o formali (ad esempio analisi di costo-efficacia e esplicita identificazione di tecnologie di cui si propone la sostituzione o la riduzione controllata di utilizzo)

Stima di impatto economico e finanziario	1	2	3	4	5
	Impatto peggiorativo		F	Impatto migliorativo	
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di impatto economico della proposta innovativa					

3.6. Equità di accesso in termini comparativi rispetto a standard *de facto* o formali (ad esempio impatto sull'accesso al mix di tecnologie diagnostico-terapeutiche generato dall'adozione di una tecnologia innovativa)

Stima di equità di accesso	1	2	3	4	5
	Impatto peggiorativo		F	Impatto migliorativo	
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di equità di accesso della proposta innovativa					

3.7. Impatto sociale ed etico rispetto a standard *de facto* o formali (ad esempio analisi qualitative di gradimento e accettabilità ovvero implicazioni non immediatamente evidenti che derivano dall'uso delle tecnologie)

Stima di impatto sociale ed etico	1	2	3	4	5
	Impatto peggiorativo		F	Impatto migliorativo	
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di impatto sociale ed etico della proposta innovativa					

3.8. Impatto organizzativo rispetto a standard *de facto* o formali (ad esempio fattori collegati all'implementazione e al mantenimento in uso delle tecnologie)

Stima di impatto organizzativo	1	2	3	4	5
	Impatto peggiorativo		F	Impatto migliorativo	
Descrizione dello standard (<i>de facto</i> o formale) considerato ai fini del giudizio di impatto organizzativo della proposta innovativa					

4. **Calcolo di un punteggio globale di priorità**

Al termine della valutazione individuale viene elaborata una sintesi dei giudizi raccolti durante la seduta. Tale sintesi correda l'esito della richiesta di ammissione alla valutazione di tecnologia sanitaria, che può essere uno dei seguenti:

- 1) richiesta di valutazione ammessa con priorità da 1 a 3:
- a. Priorità 1 = rapporto di valutazione tecnologico atteso entro 4 mesi,

b. Priorità 2 = rapporto di valutazione tecnologico atteso entro 8 mesi,

c. Priorità 3 = rapporto di valutazione tecnologico atteso entro 12 mesi;
- 2) richiesta di valutazione ammissibile previa verifica di integrazione informativa, a carico del soggetto richiedente;
- 3) richiesta di valutazione non ammessa.

La procedura di ammissione alla valutazione viene verbalizzata e l'esito è trasmesso alla Direzione Generale Sanità per i successivi adempimenti.

5. **Attribuzione di una stima di incertezza**

Ai fini di assicurare una ottimale documentazione del processo di valutazione dell'ammissibilità delle richieste di valutazione tecnologica sanitaria, il grado di concordanza (elaborato successivamente alla riunione) tra i componenti del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse viene considerato quale indicatore del livello globale di incertezza della valutazione multidimensionale e collegiale effettuata.

Stima della incertezza della tecnologia proposta riguardo a:	1	2	3	4	5	6	7	8	9	10
	Massima incertezza					F	Massima certezza			
Rilevanza tecnica										
Sicurezza										
Efficacia nella ricerca clinica										
Efficacia nella pratica										
Impatto economico										
Equità di accesso										
Impatto sociale ed etico										
Impatto organizzativo										

6. **Rappresentazione delle priorità e delle incertezze tramite grafici cumulativi**

Per le richieste ammesse alla valutazione con giudizio esplicito di priorità vengono elaborati da parte della Direzione Generale Sanità, successivamente alla riunione, grafici multidimensionali al fine di facilitare l'identificazione di aree (ad es. patologie o tecnologie) meritevoli di maggiore intensità di valutazione.

Le elaborazioni vengono restituite ai componenti del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse per via elettronica entro quattordici giorni dal termine della riunione, al fine di raccogliere eventuali osservazioni integrative.

La fase A (Identificazione delle necessità di valutazione e delle priorità per il sistema sanitario) termina con l'inserimento degli esiti del giudizio di ammissibilità alla valutazione (comprensivo del punteggio globale di priorità, dell'elaborazione del livello globale di incertezza e della identificazione di aree meritevoli di approfondimento) nel database delle richieste approvate di valutazione di tecnologie sanitarie.

Fase B – Reperimento sistematico ed analisi coerente delle documentazioni di efficacia disponibili (o identificazione della carenza di documentazione)

7. Raccolta delle documentazioni scientifiche e delle osservazioni pratiche

I soggetti accreditabili ai fini della presentazione di richieste di valutazione di tecnologie sanitarie presentano, contestualmente alla richiesta di valutazione di tecnologia sanitaria, una documentazione completa esclusivamente per via elettronica attraverso il sistema informativo predisposto dalla Direzione Generale Sanità.

La documentazione comprende copia dei lavori scientifici (opportunamente sottoposta a *copyright clearance* nel caso di letteratura ad abbonamento) da qualsiasi archivio documentale:

- archivi informatizzati sulla letteratura scientifica pubblicata;
- archivi informatizzati sui dati clinici e amministrativi;
- estratti e monografie sull'argomento;
- inventari speciali;
- riviste specializzate;
- informazioni da archivi interni o di terzi (previa soddisfazione degli eventuali diritti);
- informazioni da altre fonti.

La documentazione deve essere fornita secondo le specifiche riportate all'allegato 3 della presente delibera (A – PROPOSTA DI VALUTAZIONE DI TECNOLOGIA INNOVATIVA IN AMBITO SANITARIO).

8. Sintesi dei dati principali desumibili dalle documentazioni scientifiche e dalle osservazioni pratiche

Per ogni documento presentato ai fini del giudizio di ammissione alla valutazione i soggetti richiedenti curano la compilazione di un rapporto sintetico predisposto secondo le specifiche riportate all'allegato 3 della presente delibera (B – DOCUMENTAZIONE DA ALLEGARE).

9. Commissione di valutazioni specifiche ad esperti accreditati e valutati riguardo al possibile conflitto di interessi specifico (in atto o potenziale)

In coerenza con le procedure descritte nell'allegato 5 (Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse. Regole di procedura), il Nucleo di Valutazione dei Conflitti di Interesse identifica, nell'elenco di possibili esperti realizzato attraverso l'invito pubblico rivolto agli operatori interessati secondo le procedure previste all'allegato 3, un congruo numero di candidati esperti ai fini della analisi e della valutazione delle documentazioni in precedenza avanzate dai soggetti richiedenti.

La lista degli esperti individuati viene comunicata alla Direzione Generale Sanità che provvede ad informare per via elettronica gli esperti identificati.

In seguito alla conferma, per via elettronica, da parte degli esperti identificati, della disponibilità al coinvolgimento nell'attività di valutazione prevista, la Direzione Generale Sanità effettua una convocazione personale al fine di:

- sottoscrivere uno specifico impegno alla realizzazione della valutazione richiesta;
- rinnovare la Dichiarazione Pubblica di Interessi;
- rinnovare l'Impegno alla Riservatezza;
- ritirare le istruzioni per l'accesso alla documentazione elettronica concernente la specifica richiesta di valutazione tecnologica.

10. Interpretazione delle documentazioni scientifiche e delle osservazioni pratiche da parte degli esperti accreditati e valutati riguardo al rispettivo conflitto di interesse

Gli esperti identificati dal Nucleo di Valutazione dei Conflitti di Interesse ai fini dell'esame di una specifica richiesta di valutazione tecnologica accedono personalmente e a distanza (per via elettronica) all'intera documentazione presentata dai soggetti richiedenti. La natura dei soggetti richiedenti (enti profit o no profit) viene rivelata agli esperti, ma nessuna altra informazione (denominazione, categoria di appartenenza ecc.) viene fornita.

Gli esperti possono avanzare alla Direzione Generale Sanità richiesta di ulteriore documentazione, specificandone gli estremi. La richiesta viene girata ai soggetti richiedenti da parte della Direzione Generale Sanità.

Gli esperti possono altresì eseguire in proprio le ricerche documentali ritenute necessarie e possono consultare fonti esterne, curando in ogni caso il mantenimento della riservatezza delle informazioni loro affidate riguardo alla procedura di valutazione, secondo quanto predisposto nell'allegato 4 della presente delibera.

Gli esperti identificati realizzano la valutazione richiesta secondo i criteri, le regole di procedura ed il formato atteso stabiliti con il previsto decreto della Direzione Generale Sanità, in particolare:

- codificano la documentazione presentata secondo i livelli di documentazione di efficacia e di forza delle raccomandazioni;
- identificano eventuali specifiche valutazioni pregresse realizzate da parte di organismi nazionali o internazionali;
- valutano il grado di aggiornamento e la affidabilità delle eventuali specifiche valutazioni pregresse;
- valutano ogni altra informazione disponibile;
- esprimono una valutazione personale sintetica riguardo al livello globale della documentazione di efficacia esaminata e riguardo alla forza di raccomandazione **(2)** della specifica tecnologia sanitaria, utilizzando anche le seguenti griglie

(2) Per approfondimenti: Programma Nazionale Linee Guida. Manuale metodologico (2002-2004), capitolo 8. Disponibile all'indirizzo: <http://www.snlg-iss.it/cms/metodo>.

multidimensionali su scala ordinale con livelli predefiniti (coerenti con il sistema di *grading* adottato) per ognuna delle otto dimensioni considerate:

LIVELLO DI DOCUMENTAZIONE DI EFFICACIA

Livello globale di documentazione di efficacia della tecnologia proposta riguardo a:	6 (basso)	5	4	3	2	1 (alto)
Rilevanza tecnica						
Sicurezza						
Efficacia nella ricerca clinica						
Efficacia nella pratica						
Impatto economico						
Equità di accesso						
Impatto sociale ed etico						
Impatto organizzativo						

FORZA DELLE RACCOMANDAZIONI

Probabilità globale, data la documentazione disponibile, che l'applicazione pratica della tecnologia sanitaria esaminata determini un effettivo miglioramento dello stato di salute della popolazione target, riguardo a:	E (bassa)	D	C	B	A (alto)
Rilevanza tecnica					
Sicurezza					
Efficacia nella ricerca clinica					
Efficacia nella pratica					
Impatto economico					
Equità di accesso					
Impatto sociale ed etico					
Impatto organizzativo					

11. Sintesi e consolidamento di valutazioni specifiche comparative

Al termine della fase di valutazione personale gli esperti, utilizzando il gestionale elettronico predisposto dalla Direzione Generale Sanità, accedono all'elenco delle valutazioni prodotte dai colleghi coinvolti e vengono convocati per un incontro in Direzione Generale Sanità al fine di sintetizzare gli esiti della valutazione condotta ed integrarla con osservazioni aggiuntive ove necessario.

Al termine della riunione, e in casi particolari previo successivi confronti, redigono un rapporto sintetico nella forma di Valutazione di Efficacia Comparata ovvero di Scheda di Valutazione di Tecnologia Sanitaria. Tale rapporto viene aggiunto alle valutazioni personali ed alla documentazione raccolta nel gestionale elettronico.

Copia elettronica della sintesi e delle singole valutazioni realizzate dagli esperti viene trasmessa a cura della Direzione Generale Sanità ai soggetti proponenti la valutazione, assieme all'invito a produrre eventuali osservazioni, integrazioni o direzioni-deduzioni, corredate da ogni documentazione ritenuta necessaria, entro il termine di dieci giorni lavorativi a partire dalla data di inoltro della sintesi e delle singole valutazioni.

Fase C – Valutazione critica delle documentazioni di efficacia, comprensiva del giudizio circa il significato pratico (applicazione) nella prospettiva del sistema sanitario

12. Esame delle valutazioni comparative e formulazione delle raccomandazioni di uso

La Direzione Generale Sanità predispone all'ordine del giorno delle riunioni del Tavolo Tecnico per l'Appropriatezza in Medicina l'elenco delle valutazioni tecnologiche sanitarie (sintesi e valutazioni singole) realizzate dagli esperti identificati e ne fornisce le indicazioni di accesso elettronico alla documentazione completa, entro 2 mesi dalla data di convocazione del Tavolo Tecnico.

Le osservazioni eventualmente ricevute, sempre per via elettronica, da parte dei soggetti richiedenti la valutazione in seguito all'esame della sintesi e delle singole valutazioni realizzate dagli esperti, vengono contestualmente trasmesse al Tavolo Tecnico per l'Appropriatezza in Medicina.

Durante le riunioni del Tavolo Tecnico le Valutazioni di Efficacia Comparate e le Schede di Valutazione di Tecnologia Sanitaria, nonché le eventuali osservazioni integrative prodotte dagli enti richiedenti, vengono presentate brevemente (20' massimo) da parte di un esperto accreditato, il quale può avvalersi della documentazione completa inserita per via elettronica e della collaborazione degli altri esperti che hanno partecipato alla valutazione.

Al termine della presentazione e dopo aver risposto ad eventuali richieste di chiarimento l'esperto abbandona la seduta e resta a disposizione per eventuali ulteriori delucidazioni.

I componenti del Tavolo Tecnico per l'Appropriatezza in Medicina effettuano una comparazione tra gli esiti del giudizio di priorità ed ammissibilità alla valutazione, emesso dal Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse in fase di approvazione della richiesta, con gli esiti del processo di valutazione sintetizzati nei rapporti presentati.

Il Tavolo Tecnico per l'Appropriatezza in Medicina procede quindi alla approvazione della valutazione espressa emettendo un giudizio di raccomandazione di uso ai fini delle decisioni allocative (tariffe di rimborso), applicative (intensità e frequenza di prescrizione ed impiego) e valutative (ad es. audit clinici, o controlli esterni, di appropriatezza specifica per percorso diagnostico-terapeutico complessivo).

Tale giudizio viene sintetizzato avvalendosi di tabelle riassuntive, sull'esempio di quelle sotto riportate, accompagnate da integrazioni secondo necessità e dalla documentazione raccolta e valutata, come.

DOCUMENTAZIONE DI EFFICACIA

Livello globale di documentazione di efficacia della tecnologia:	6 (basso)	5	4	3	2	1 (alto)
(Denominazione e codifica della tecnologia sanitaria, della patologia e, quando sarà disponibile, del nodo del percorso di riferimento riportato Mappa della Medicina on-line)						

FORZA DELLE RACCOMANDAZIONI

Probabilità globale, data la documentazione disponibile, che l'applicazione pratica della tecnologia sanitaria esaminata determini un effettivo miglioramento dello stato di salute della popolazione target	E (bassa)	D	C	B	A (alta)
(Denominazione e codifica della tecnologia sanitaria, della patologia e, quando sarà disponibile, del nodo del percorso di riferimento riportato Mappa della Medicina on-line)					

13. Disseminazione dei risultati e delle raccomandazioni di uso

Le valutazioni comparative e le raccomandazioni di uso approvate dal Tavolo Tecnico per l'Appropriatezza in Medicina costituiscono riferimento specifico per numerose attività di programmazione, gestione e valutazione all'interno di settori differenti del Servizio Sanitario Regionale, e specificamente:

- vengono comunicate agli enti (IReF, AA.SS.LL., AA.OO., Fondazioni IRCCS, soggetti erogatori accreditati di diritto privato) deputati all'aggiornamento e alla gestione operativa degli obiettivi di interesse regionale della formazione continua secondo il modello lombardo di ECM-CPD, per la voce «Programma di formazione regionale sulla Valutazione delle Tecnologie Sanitarie»;
- contribuiscono ad assolvere al debito formativo (per la quota associata agli obiettivi di interesse regionale e nella forma di Formazione sul Campo in forma Integrata, tipologia «Partecipazione a gruppi di miglioramento») dei soggetti che hanno contribuito al processo di valutazione (esperti accreditati e attivamente coinvolti) e ne costituiscono elemento qualificante del portfolio summativo-formativo;
- alle ASL, AO e Fondazioni IRCCS è demandato l'inserimento, nell'annuale Piano di Formazione Aziendale (e l'integrazione al Piano già predisposto per l'anno 2008), di una voce di progetto denotata «Formazione continua sulla Valutazione delle Tecnologie Sanitarie», nonché la registrazione delle attività in presenza realizzate dal professionista quale contributo individuale al processo di elaborazione di Schede di Valutazione di Tecnologia Sanitaria;
- costituiscono specifico contributo per l'aggiornamento dinamico dei contenuti della Mappa della Medicina on-line di Regione Lombardia (nodi informativi e testi allegati);
- costituiscono specifico contributo informativo di riferimento (cfr. Allegato 5: Farmaceutica e Protesica – d.g.r. n. 8/5743 del 31 ottobre 2007, «Determinazioni in ordine alla gestione del Servizio Socio Sanitario Regionale per l'esercizio 2008 (di concerto con l'Assessore Abelli)»:
 - ai fini della valutazione, da parte delle ASL, del mix di prescrizioni appropriate per l'iter diagnostico-terapeutico di riferimento;
 - ai fini della promozione di Percorsi Diagnostico-Terapeutici condivisi tra ASL e AO per uso appropriato di farmaci in patologie croniche ad alto costo (esempio BPCO, HIV, artrite reumatoide, ecc.);
 - ai fini della condivisione tra AO/Fondazioni e ASL di prontuari alla dimissione, in cui saranno valutate le iniziative aziendali tese a diffondere tra gli operatori sanitari (clinici e farmacisti) l'uso e la prescrizione alla dimissione dei farmaci equivalenti (in particolare ATC: A02, C10, C09, C08, N06, J01);
 - ai fini della promozione di iniziative di informazione e di formazione specifica per i medici prescrittori del territorio e delle strutture ospedaliere relativamente ai farmaci di maggiore utilizzo e finalizzate alla appropriatezza prescrittiva intesa come corretto dosaggio di farmaco prescritto e continuità temporale di adesione alla terapia (cosiddetta persistenza) dei pazienti;
- costituiscono contributo informativo per le attività di contrattazione decentrata e di determinazione aziendale degli Accordi di Governo Clinico per la Medicina Generale e la Pediatria di libera scelta;
- costituiscono contributo informativo per le attività aziendali previste da parte dei Collegi di Direzione e dei Consigli dei Sanitari delle AA.OO. e delle Fondazioni, nonché per le attività previste da parte degli organismi gestionali dei Piani di settore e di Sviluppo (Oncologico, Cerebrocardiovascolare, ecc.) di cui all'allegato 6 della d.g.r. n. 8/5743 del 31 ottobre 2007 «Determinazioni in ordine alla gestione del Servizio Socio Sanitario Regionale per l'esercizio 2008».

14. Controllo dell'impatto ottenuto dalle raccomandazioni di uso

La verifica degli impatti ottenuti dalle valutazioni comparative e dalle raccomandazioni di uso approvate dal Tavolo Tecnico per l'Appropriatezza in Medicina e implementate con le azioni informative, formative e gestionali richiamate al punto precedente, verrà regolamentata da successivo decreto della Direzione Generale Sanità, previsto dalla presente delibera. Ciò previa valutazione delle informazioni che saranno raccolte tramite l'analisi degli archivi informativi specifici (elenchi di richieste di valutazione di tecnologie sanitarie; elenchi di valutazioni realizzate; elenchi di valutazioni e raccomandazioni di uso approvate), e le analisi della Banca dati Assistito e degli altri strumenti a disposizione della programmazione regionale in materia.

SCHEMA TIPO DI MODULISTICA ELETTRONICA
PER PROPOSTE DI VALUTAZIONE DI TECNOLOGIE SANITARIE

A) PROPOSTA DI VALUTAZIONE DI TECNOLOGIA INNOVATIVA IN AMBITO SANITARIO

Denominazione del soggetto che propone la valutazione tecnologica:

.....
.....

Indirizzo del legale rappresentante:

.....
.....

Tel. Fax E-mail

Sito web

Tipologia del soggetto proponente:

☐ Ente <i>profit</i>	☐ Ente <i>no profit</i>
☐ Azienda Farmaceutica	☐ Azienda Sanitaria Locale del SSR
☐ Piccola e Media Impresa del settore delle biotecnologie	☐ Azienda Ospedaliera del SSR
☐ Altra tipologia <i>profit</i>	☐ Fondazione del SSR
	☐ Altro soggetto accreditato erogatore di prestazioni a carico del SSR
	☐ Università avente sede in Regione Lombardia
	☐ Società Scientifica avente sede in Regione Lombardia
	☐ Ordine Professionale
	☐ Altra tipologia <i>no profit</i>

Denominazione della tecnologia per cui si propone la valutazione:

.....
.....
.....

Codifiche rilevanti per la tecnologia:

- ATC:
- CND:
- MeSH (italiano – campo obbligatorio):
- AIC (Autorizzazione all’Immissione in Commercio) per farmaci:
- Certificazione di marcatura CE per dispositivi biomedicali:

Elenco delle schede tecniche allegate:

.....
.....
.....

Descrizione del processo diagnostico-terapeutico entro cui si colloca l'utilizzo della tecnologia da valutare:

.....

.....

.....

.....

Codifiche rilevanti per il processo diagnostico-terapeutico:

- ICD9:
-
-
- SNOMED:
-
-
- TNM:
-
-
- MeSH (italiano):
-
-

Numerosità di prestazioni annue previste a carico del SSR:

- Numero di procedure
- Numero di soggetti beneficiari
- Numero di operatori sanitari interessati

Elenco della documentazione di supporto per la valutazione della tecnologia proposta:

Tipologia	Numero di documenti	Nome file dei documenti allegati in copia (testo completo)
Studi clinici randomizzati con controlli contemporanei ad ampia casistica		
Studi clinici randomizzati con controlli contemporanei a casistica limitata		
Studi clinici non randomizzati con controlli contemporanei		
Studi clinici non randomizzati con controlli storici		
Studi naturalistici		
Studi osservazionali/naturalistici (a coorti, caso-controllo)		
Studi trasversali		
Audit clinici		
Studi di sorveglianza		
Studi di costo-efficacia		
Dati non ancora pubblicati ed autocertificati di pregresse esperienze applicative sperimentali e/o cliniche		
Rapporti di valutazione di tecnologie sanitarie predisposti da altre organizzazioni		
Altri studi		

Denominazione, eventuali codifiche (ATC, CND, MeSH, ICD9, SNOMED, TNM, altra) e descrizione delle tecnologie attualmente impiegate nella pratica (standard *de facto* o formali) di cui la tecnologia proposta per la valutazione viene proposta quale sostituto parziale/totale, a parità di frequenza ed intensità di prescrizione nella popolazione target,

rispetto alle seguenti otto dimensioni di impatto (tecnico, sicurezza, efficacia teorica e pratica, economico, di accessibilità, sociale, etico ed organizzativo):

A) Rilevanza tecnica
1. Denominazione della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo alla rilevanza tecnica
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente la rilevanza tecnica della tecnologia proposta

B) Sicurezza
1. Descrizione esplicita della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo alla sicurezza
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente la sicurezza della tecnologia proposta

C) Efficacia nel contesto di ricerca clinica
1. Denominazione della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo alla efficacia nel contesto di ricerca clinica
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente l'efficacia nel contesto di ricerca clinica della tecnologia proposta

Ad esempio: studi clinici randomizzati controllati, studi a coorti, studi caso-controllo.

D) Efficacia nel contesto della medicina pratica
1. Descrizione esplicita della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo alla efficacia nel contesto della medicina pratica
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente l'efficacia nel contesto della medicina pratica della tecnologia proposta

Ad esempio: audit clinici, studi di sorveglianza, studi osservazionali/naturalistici

E) Impatto economico
1. Descrizione esplicita della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo all'impatto economico
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente l'impatto economico della tecnologia proposta

Ad esempio: audit clinici, studi di costo-efficacia

F) Equità di accesso
1. Descrizione esplicita della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo all'equità di accesso
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente l'equità di accesso alla tecnologia proposta

G) Impatto sociale ed etico
1. Descrizione esplicita della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo all'impatto sociale ed etico
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente l'impatto sociale ed etico della tecnologia proposta

H) Impatto organizzativo
1 Descrizione esplicita della tecnologia di riferimento (standard <i>de facto</i> o formale) cui si propone di indirizzare la valutazione comparativa richiesta riguardo all'impatto organizzativo
2. Codifiche
3. Descrizione esplicita
4. Elenco della documentazione concernente l'impatto organizzativo della tecnologia proposta

Data
 Firma del Legale Rappresentante

B) DOCUMENTAZIONE DA ALLEGARE

- Riassunto esecutivo** per il Tavolo Tecnico per l'Appropriatezza in Medicina (massimo 1 pagina formato A4 con 60 righe di 60 battute ciascuna) comprendente la descrizione di:
 - stima del costo incrementale del programma innovativo (I) rispetto al costo di trattamento attuale del medesimo numero di pazienti in assenza del programma (I);
 - stima del risparmio incrementale ottenibile dalla cancellazione del programma tradizionale (T) per il medesimo numero di pazienti;
 - stima del beneficio incrementale ottenibile con l'impiego del programma (I) rispetto al beneficio garantito al medesimo numero di pazienti in assenza del programma (I) e cioè tramite l'impiego del programma tradizionale (T);
 - stima del beneficio decrementale associato alla cancellazione del programma tradizionale (T), in previsione del beneficio garantito al medesimo numero di pazienti dall'implementazione del programma innovativo (I).

Per le predette stime si intendono i valori di posizione (media, mediana, ecc.) e di dispersione (quartili, deviazioni standard, intervalli di confidenza ecc.) desunti da metanalisi o revisioni sistematiche o studi controllati o altra documentazione disponibile ed allegata in copia, con particolare attenzione per gli studi atti a documentare i rapporti costo / opportunità e costi / benefici marginali;

 - indicatori proposti al fine di monitorare l'impatto nella pratica dell'implementazione del programma innovativo (I) in sostituzione del programma tradizionale (T).
- Presentazione** in formato PowerPoint o open (massimo 5 diapositive) per il Tavolo Tecnico per l'Appropriatezza in Medicina.
- Documentazione scientifica** di supporto in copia (il cui *nomefile* è riportato nella tabella «Elenco della documentazione di supporto»).

**INVITO A PRESENTARE CANDIDATURE IN VISTA DELLA COSTITUZIONE DI UN ELENCO
DI ESPERTI PER LA VALUTAZIONE DELLE TECNOLOGIE SANITARIE. DICHIARAZIONE PUBBLICA
DI INTERESSI E IMPEGNO ALLA RISERVATEZZA PER COMPONENTI DEL TAVOLO TECNICO REGIONALE
PER L'APPROPRIATEZZA IN MEDICINA E PER ESPERTI**

Col programma di valutazione delle tecnologie sanitarie la Regione Lombardia intende soddisfare la crescente necessità di verifica dell'efficienza e dell'appropriatezza specifica delle prestazioni e delle tecnologie innovative in ambito sanitario, nel rispetto dell'erogazione dei Livelli essenziali di Assistenza.

Obiettivo generale del programma regionale lombardo di valutazione delle tecnologie sanitarie è facilitare la diffusione nella pratica clinica delle tecnologie più efficaci, sicure ed efficienti in sostituzione di tecnologie meno efficaci, sicure ed efficienti, secondo modalità responsabili, condivise, trasparenti, monitorabili e verificabili.

Il programma è finalizzato alla valutazione di quelle tecnologie innovative in campo sanitario che abbiano già concluso, in base alle normative vigenti, l'iter di sperimentazione clinica e che siano già in possesso dei certificati di autorizzazione all'immissione in commercio ovvero del marchio CE, secondo le dimensioni:

- della documentazione di efficacia (raggiungimento di risultati dimostrabili mediante evidenze scientifiche in termini di riduzione di recidive e/o di morbosità e/o di morbidità e/o di mortalità e/o di maggiore sicurezza);
- dell'efficienza allocativa (miglioramento dell'efficienza di erogazione dei servizi sanitari);
- della qualità e dell'appropriatezza di erogazione dei servizi.

La Direzione Generale Sanità invita i professionisti della salute operanti sul territorio lombardo in qualità di dipendenti o convenzionati con le AA.SS.LL. o con gli enti erogatori del Servizio Sanitario Regionale (Aziende Ospedaliere, Fondazioni, Università) a presentare la propria candidatura ai fini della costituzione di un elenco di esperti accreditati i quali, previa valutazione dei possibili conflitti di interesse specifici, possano essere chiamati a produrre rapporti di valutazione ed analisi di impatto delle tecnologie sanitarie.

La presentazione delle candidature avviene esclusivamente per via elettronica tramite l'apposito sistema gestionale che verrà predisposto e prevede la compilazione di una Dichiarazione Pubblica di Interessi e di un Impegno alla Riservatezza nonché il deposito, sempre per via elettronica esclusiva, della documentazione di supporto in formato di allegati al modulo di candidatura:

- *curriculum vitae* in formato europeo in due versioni: in lingua italiana ed in lingua inglese;
- codifica delle proprie competenze attraverso:
 - 1) l'elenco dei settori scientifico-disciplinari di cui al DM MURST del 4 ottobre 2000 (G.U. n. 249 del 24 ottobre 2000 - Supplemento Ordinario 175) (1) e successive modifiche; ELENCO DEI SETTORI SCIENTIFICO-DISCIPLINARI;
 - 2) il soggettario MeSH (*Medical Subject Headings*) in versione italiana, che verrà reso disponibile nel sistema informativo di supporto predisposto dalla Direzione Generale Sanità;
- autocertificazione del diploma di laurea;
- autocertificazione di eventuale diploma di specializzazione;
- autocertificazione del rapporto di dipendenza o di convenzione con ASL, AO, Fondazioni o Università aventi sede in Regione Lombardia.

Qualora non siano forniti tali documenti o il modulo di candidatura non contenga tutte le informazioni necessarie come delineate precedentemente, al candidato viene notificata la non completezza della documentazione e viene richiesto l'inoltro, sempre tramite il gestionale per l'accreditamento di esperti, del materiale o dei documenti mancanti entro i successivi 30 giorni dalla comunicazione. La valutazione della domanda non ha inizio finché non siano stati forniti tutti i documenti e le informazioni necessarie.

In carenza di documentazione la candidatura avanzata è considerata respinta e viene archiviata in un apposito elenco.

La reiterazione della candidatura all'accreditamento regionale di esperti per la valutazione di tecnologie sanitarie da parte di candidati che non hanno fornito completa documentazione è inibita per un successivo periodo di un anno.

Compiti degli esperti accreditati che verranno selezionati per le valutazioni specifiche sono:

1. esaminare le documentazioni scientifiche presentate dai soggetti abilitati a corredo delle richieste di valutazione;
2. raccogliere ed elaborare ogni ulteriore documentazione ritenuta necessaria a proprio giudizio;
3. contribuire alla predisposizione di Schede di Valutazione di Tecnologia Sanitaria oppure Valutazioni di Efficacia Comparata, anche secondo procedure a distanza (on-line) mirate a garantire, nei limiti del possibile, l'espressione in cieco di pareri multipli con criteri di multidisciplinarietà e multiprofessionalità;
4. supportare la Direzione Generale Sanità nella implementazione di regolamentazioni mirate alla diffusione, responsabile e condivisa, di tecnologie innovative e costo-efficaci in sostituzione di tecnologie meno efficaci, sicure ed efficienti, anche tramite la partecipazione, in qualità di relatori, a convegni e corsi di formazione, e tramite la realizzazione di opere derivate (brevi manuali, materiale divulgativo, ecc.). Queste rimarranno di proprietà di Regione Lombardia e saranno liberamente utilizzabile da terzi, fatta salva specifica diversa espressione, nell'ambito della licenza *Creative Commons* «Attribuisci e Condividi allo stesso modo 3.0 (e versioni successive) (2)» che promuove il riutilizzo delle produzioni intellettuali di pubblico dominio tutelando l'attribuzione degli autori (*authorship*) e proibendo la commercializzazione, la produzione di lavori derivati e la distribuzione non espressamente autorizzata.

(1) Disponibile all'indirizzo: http://sito.cineca.it/murst-daus/settori2000/settori_discipline.html.

(2) Disponibile alla locazione: <http://creativecommons.org/licenses/by-sa/3.0/deed.it>. Consultato il 15 gennaio 2008.

VALUTAZIONE DELLE TECNOLOGIE SANITARIE.
DICHIARAZIONE PUBBLICA DI INTERESSI E IMPEGNO ALLA RISERVATEZZA
PER COMPONENTI DEL TAVOLO TECNICO REGIONALE PER L'APPROPRIATEZZA
IN MEDICINA E PER ESPERTI

Questo documento consiste di due parti, la Dichiarazione Pubblica di Interessi e l'Impegno alla Riservatezza. Entrambe le parti devono essere debitamente compilate. **Tutte le pagine devono essere firmate e datate.** Se il documento è compilato a mano, assicurarsi che le informazioni richieste siano redatte in modo chiaro.

A) DICHIARAZIONE PUBBLICA DI INTERESSI

Il sottoscritto, (Titolo) **(Nome)** **(Cognome)**

Nazionalità

Organizzazione/Azienda

Indirizzo professionale

Email

con il presente documento dichiara che, a sua conoscenza, gli unici interessi diretti o indiretti, nell'industria farmaceutica, biotecnologica, informatica e delle tecnologie sanitarie sono i seguenti: *(Selezionare tutte le caselle e specificare il nome dell'azienda e del prodotto in caso di interesse dichiarato¹. Se necessario, utilizzare fogli aggiuntivi, firmati e datati).*

Tabella 1

Attività di una azienda in relazione a un particolare prodotto/gruppo di prodotti	No	Attualmente o nell'anno passato	Da più di 1 anno fa fino a 5 anni fa	Più di 5 anni fa ²
Dipendente	☐	☐	☐	☐
Consulente ³	☐	☐	☐	☐
Coordinatore ⁴	☐	☐	☐	☐
Membro di comitato direttivo, assemblea consultiva o organo equivalente	☐	☐	☐	☐
Collaboratore per lo sviluppo di un prodotto ⁵	☐	☐	☐	☐

1 Se vengono selezionate le caselle nelle colonne più scure (interessi dichiarati), è necessario fornire ulteriori informazioni a pagina 2 riguardo l'azienda e i prodotti coinvolti. Se vengono dichiarati interessi nella Tabella 1, ma non vengono fornite le relative informazioni nella seconda pagina, il modulo verrà rispedito al mittente per il completamento.

2 Questa informazione non verrà utilizzata nella valutazione degli interessi dichiarati, ma sarà utile nel contesto di una migliore trasparenza riguardo interessi precedenti.

3 Un consulente è un esperto remunerato per la fornitura di consulti o servizi in un campo particolare.

Data.....
Firma.....

	Periodo di attività	Azienda	Prodotti Inserire tutti i prodotti per cui si è avita la responsabilità principale	Indicazioni terapeutiche
Dipendente				

	Periodo di attività	Azienda	Prodotti Inserire tutti i prodotti per cui si è avita la responsabilità principale	Indicazioni terapeutiche
Consulente				

	Periodo di attività	Azienda	Area di attività/prodotto	Indicazioni terapeutiche
Membro di comitato direttivo, assemblea consultiva o organo equivalente				

	Periodo di attività	Azienda	Prodotti	Indicazioni terapeutiche
Coordinatore				

4 Si definisce **coordinatore**, per gli scopi di questo documento, un agente responsabile del coordinamento di agenti che partecipano a un trial multicentrico.

5 Si definisce **collaboratore**, per gli scopi di questo documento, un agente che partecipa a un trial multicentrico.

Data.....

Firma.....

	Periodo di attività	Azienda	Prodotti	Indicazioni terapeutiche
Collaboratore				

Ho interessi finanziari in una azienda farmaceutica, biotecnologica, informatica e delle tecnologie sanitarie per	NO	SI	Azienda
più di 50,000 euro o pari (esclusi fondi di investimento)	☐	☐	
meno di 50,000 euro o pari (esclusi fondi di investimento)	☐	☐	

	NO	SI	Azienda
Possiedo il brevetto di un prodotto	☐	☐	
	NO ovvero non ne sono a conoscenza ⁶	SI	Azienda
L'organizzazione di cui sono dipendente riceve una sovvenzione o altri finanziamenti da parte di una azienda farmaceutica (da cui non ho beneficio personale) ⁷	☐	☐	

6 Nel caso specifico mi impegno fin d'ora, in caso di selezione in qualità di esperto ai fini della valutazione di una specifica tecnologia, a facilitare Regione Lombardia nell'ottenimento, da parte della organizzazione di cui sono dipendente o con cui sono convenzionato, della documentazione di sovvenzioni o finanziamenti riferibili a industrie o società, anche detentrici del pacchetto di controllo di società controllate, direttamente connesse con la tecnologia oggetto della valutazione.

7 Escluse le tariffe pagate dalle industrie farmaceutiche o biotecnologiche per la valutazione del lavoro intrapreso dalle Autorità nazionali competenti.

Data.....
 Firma.....

Oltre agli interessi qui dichiarati, con questo documento il sottoscritto dichiara di non avere alcun altro interesse e che non ci sono ulteriori fatti di cui dovrebbero essere a conoscenza la Regione Lombardia e il pubblico.
In caso di altri interessi o fatti, si prega di specificarli:

In caso di cambiamenti nelle informazioni sopra riportate, conseguenti ad interessi addizionali sopravvenuti, il sottoscritto li notificherà sollecitamente a Regione Lombardia e compilerà una nuova Dichiarazione di Interessi fornendo dettagli sui cambiamenti. Questa dichiarazione non esonera il sottoscritto dall'obbligo di dichiarare qualunque potenziale conflitto di interessi nella fase iniziale di qualunque attività di Regione Lombardia⁸ a cui partecipi.

8 La dicitura “attività di Regione Lombardia” comprende qualunque riunione (inclusa la preparazione delle riunioni e il follow-up, discussioni associate o qualunque altra attività collegata) con dirigenti, quadri ed impiegati della Regione.

Data.....
Firma.....

B) IMPEGNO ALLA RISERVATEZZA

In vista delle seguenti definizioni:

La dicitura “Informazione Confidenziale” riguarda qualunque informazione, fatto, dato e ogni altra questione di cui si viene a conoscenza direttamente o indirettamente come risultanti dalle attività di Regione Lombardia.

La dicitura “Documenti Confidenziali” riguarda tutte le bozze, le informazioni preparatorie, i documenti e ogni altro materiale, insieme alle informazioni ivi contenute alle quali si ha accesso direttamente o indirettamente come risultato della partecipazione alle attività di Regione Lombardia. Inoltre, qualunque dato o nota relativi a Informazioni Confidenziali o a Documenti Confidenziali devono essere trattati come Documento confidenziale.

Il sottoscritto comprende che può essere invitato direttamente o indirettamente alla partecipazione per alcune attività di Regione Lombardia e con questo documento si impegna:

- **a trattare tutte le Informazioni Confidenziali e i Documenti Confidenziali secondo le condizioni di stretta riservatezza**
- **a non rivelare (o autorizzare altri a rivelare) in alcun modo a terzi le Informazioni Confidenziali o i Documenti Confidenziali**
- **a non usare (o autorizzare altri ad usare) le Informazioni Confidenziali e i Documenti Confidenziali per altri scopi se non il lavoro connesso alle attività di Regione Lombardia**
- **a disporre dei Documenti Confidenziali come di materiale confidenziale, nel momento in cui il sottoscritto non abbia più necessità di utilizzarli.**

Questo impegno non è limitato nel tempo, ma non è applicabile a documenti o informazioni che il sottoscritto può ragionevolmente provare fossero in suo possesso prima della data di questo impegno o che diventano di pubblico dominio in altro modo che come risultato di violazione del suddetto impegno.

Data.....

Firma.....

NUCLEO DI VALUTAZIONE DELLE PRIORITÀ E DEI CONFLITTI DI INTERESSE (NVPCI) REGOLE DI PROCEDURA

1) Mandato

Il mandato del Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse (NVPCI) comprende:

- la produzione di valutazioni tecniche di priorità, nella prospettiva del Servizio Sanitario Regionale, delle richieste di valutazione tecnologica avanzate dai soggetti accreditati secondo il processo definito nell'allegato 2;
- il supporto alla Direzione Generale Sanità nella valutazione di priorità di tecnologie sanitarie identificate anche tramite approcci di *horizon scanning*;
- la verifica della accettabilità per il coinvolgimento di componenti ed esperti nelle attività del Tavolo Tecnico per l'Appropriatezza in Medicina e negli eventuali altri gruppi di lavoro di Regione Lombardia coinvolti a vario titolo nella valutazione di tecnologie sanitarie.

2) Composizione del NVPCI

Il Nucleo di Valutazione delle Priorità e dei Conflitti di Interesse è composto da 24 membri appartenenti alla D.G. Sanità (3 componenti), agli staff direzionali delle ASL (8 componenti), delle A.O. (8 componenti) e degli IRCCS di diritto pubblico e privato (5 componenti) del sistema sanitario regionale lombardo, scelti dalla Direzione Generale Sanità sentite le Direzioni Generali delle Aziende e degli IRCCS e nominati per un periodo di tre anni.

I componenti del NVPCI devono avere esperienza scientifica nel campo della medicina umana.

Il NVPCI comprende:

- un nucleo fondamentale di 8 componenti principali (2 provenienti dalla D.G. Sanità, 2 provenienti dalle ASL, 2 dalle A.O. e 2 dagli IRCCS)
- un nucleo di appoggio costituito dagli altri 16 componenti di supporto, assegnati quali sostituti dei componenti del nucleo fondamentale (6 provenienti dalle ASL, 6 dalle A.O. e 4 dagli IRCCS).

Gli otto membri principali ruotano annualmente tra il totale dei 24 componenti, in modo tale che ciascun membro del NVPCI svolga le funzioni di componente principale per almeno uno dei tre anni di mandato. Questa rotazione è determinata all'inizio del mandato triennale e rispetta la distribuzione di provenienza (Azienda Sanitaria, Ospedaliera, IRCCS).

3) Rinnovamento dei componenti del NVPCI

Tre mesi prima del termine del mandato del NVPCI, i componenti sono invitati ad esprimere il proprio interesse nel proseguire l'attività come componenti di diritto per un ulteriore mandato triennale. La finalità è di assicurare continuità e di condividere esperienze con i componenti del nuovo NVPCI.

Tre mesi prima del termine del mandato del NVPCI, la Direzione Generale Sanità, sentite le Direzioni delle ASL, A.O. ed IRCCS, individua e nomina sedici nuovi membri (non facenti parte del NVPCI uscente, ad eccezione che per i membri della D.G. Sanità) per l'inizio del nuovo mandato triennale del NVPCI. Altri otto componenti vengono individuati e nominati tra i componenti uscenti che hanno espresso interesse al rinnovo.

Se un componente del NVPCI lascia il gruppo prima dello scadere del mandato, deve essere rimpiazzato con un componente indicato dalla stessa azienda e nominato dalla Direzione Generale Sanità.

4) Sostituzione in caso di non disponibilità dei componenti del nucleo fondamentale

Per ogni componente del NVPCI la Direzione Generale Sanità, sentita l'amministrazione di provenienza, identifica una lista «a cascata» per eventuali sostituzioni temporanee.

È responsabilità del componente principale, nell'eventualità di impedimenti a compiere la valutazione per altri impegni di lavoro, assicurare che uno dei componenti di supporto ad egli assegnato possa portare a termine la valutazione.

È responsabilità del componente di supporto informare il rispettivo componente principale (e seguire il procedimento di supporto nel sistema «a cascata») nel caso sia anch'egli non disponibile per un determinato periodo di tempo (congedi, missioni, altre assenze prevedibili).

5) Responsabilità del Presidente del NVPCI

Il Presidente del NVPCI viene **nominato dalla D.G. Sanità** tra i componenti principali del NVPCI e dura in carica per i tre anni di mandato del gruppo. Le responsabilità del Presidente sono le seguenti:

- assicurare che le risposte (valutazioni di priorità, supporto alla Direzione Generale Sanità, verifiche dei conflitti di interessi per esperti coinvolti nelle valutazioni delle tecnologie e nel Tavolo Tecnico per l'Appropriatezza in Medicina) vengano fornite per tempo
- assicurare una copertura sufficiente nella pausa estiva
- archiviare ed aggiornare i documenti elettronici
- organizzare annualmente la formazione professionale sulle procedure del NVPCI
- coinvolgere i membri del NVPCI in revisioni della procedura di verifica dei conflitti di interesse
- preparare i rapporti previsti per le U.O. e le strutture della Direzione Generale Sanità.

Il Presidente del NVPCI può delegare parte delle funzioni previste ad altri componenti principali del NVPCI.

6) Invio della richiesta di valutazione al NVPCI

La Direzione Generale Sanità inoltra al Presidente del NVPCI l'elenco delle richieste di valutazione tecnologica nonché ogni documentazione di supporto ricevuta dagli enti richiedenti ed eventualmente integrata dalla Direzione Generale Sanità stessa.

7) Archiviazione congiunta delle richieste e dei risultati delle Valutazioni Tecnologiche (Direzione Generale Sanità) e delle Valutazioni di Interesse (NVPCI)

All'interno del sistema gestionale realizzato da Direzione Generale Sanità è predisposta una cartella VTS (Valutazioni Tecnologie Sanitarie) con sottocartelle annidate e distinte per ciascun anno e per ciascun progetto specifico.

Alla ricezione di una richiesta di valutazione tecnologica sanitaria, la Direzione Generale Sanità crea una sottocartella specifica ove viene archiviata tutta la documentazione della richiesta e del successivo risultato.

All'interno della sottocartella di progetto il Presidente del NVPCI o un suo delegato cura l'archiviazione dei pareri di priorità espressi e dei risultati della valutazione di interesse effettuate dal NVPCI.

8) Catalogazione delle richieste di valutazione (e delle necessità di valutazione in aree orfane), calcolo di un punteggio globale di priorità, attribuzione di una stima di incertezza, rappresentazione delle priorità e delle incertezze tramite grafici cumulativi

Si rimanda alle corrispondenti attività (3, 4, 5, 6) descritte per la Fase A nell'allegato 2.

9) Procedura di valutazione del conflitto di interesse degli esperti

La decisione da parte del nucleo fondamentale del NVPCI è obbligatoria. Qualora l'esperto sia contemporaneamente componente del NVPCI ed esperto richiedente l'accreditamento regionale, non può partecipare alla valutazione e deve essere sostituito da un componente di supporto, secondo il sistema «a cascata» (paragrafo 4).

La valutazione da parte del NVPCI deve essere attuata, di norma, nei sette giorni seguenti la richiesta depositata on-line sul sistema informativo dedicato.

La valutazione è individuale ed effettuata a distanza da parte di ciascun componente del NVPCI. I pareri dei componenti del nucleo fondamentale del NVPCI vengono raccolti per via elettronica avvalendosi delle funzionalità di collaborazione a distanza predisposte nel sistema gestionale di supporto.

I componenti principali del NVPCI (o loro sostituti nominati) valutano la richiesta sulla base delle informazioni disponibili e di qualsiasi altra informazione venga ritenuta appropriata, purché depositata in forma elettronica all'interno del gestionale.

I componenti del NVPCI possono richiedere informazioni addizionali o chiarimenti direttamente agli esperti accreditati e sottoposti a valutazione oppure possono ottenerne tramite ricerche on-line sui prodotti (compresi i *competitor*) indicati nelle richieste di valutazione o in qualsiasi altra documentazione ritenuta pertinente. Eventuali richieste indirizzate ai soggetti richiedenti le valutazioni (indipendentemente dalla natura lucrativa o non lucrativa) verranno avanzate alla Direzione Generale Sanità che provvederà all'inoltro curando l'anonimizzazione della richiesta.

La procedura di valutazione comprende le seguenti fasi, illustrate nel grafico:

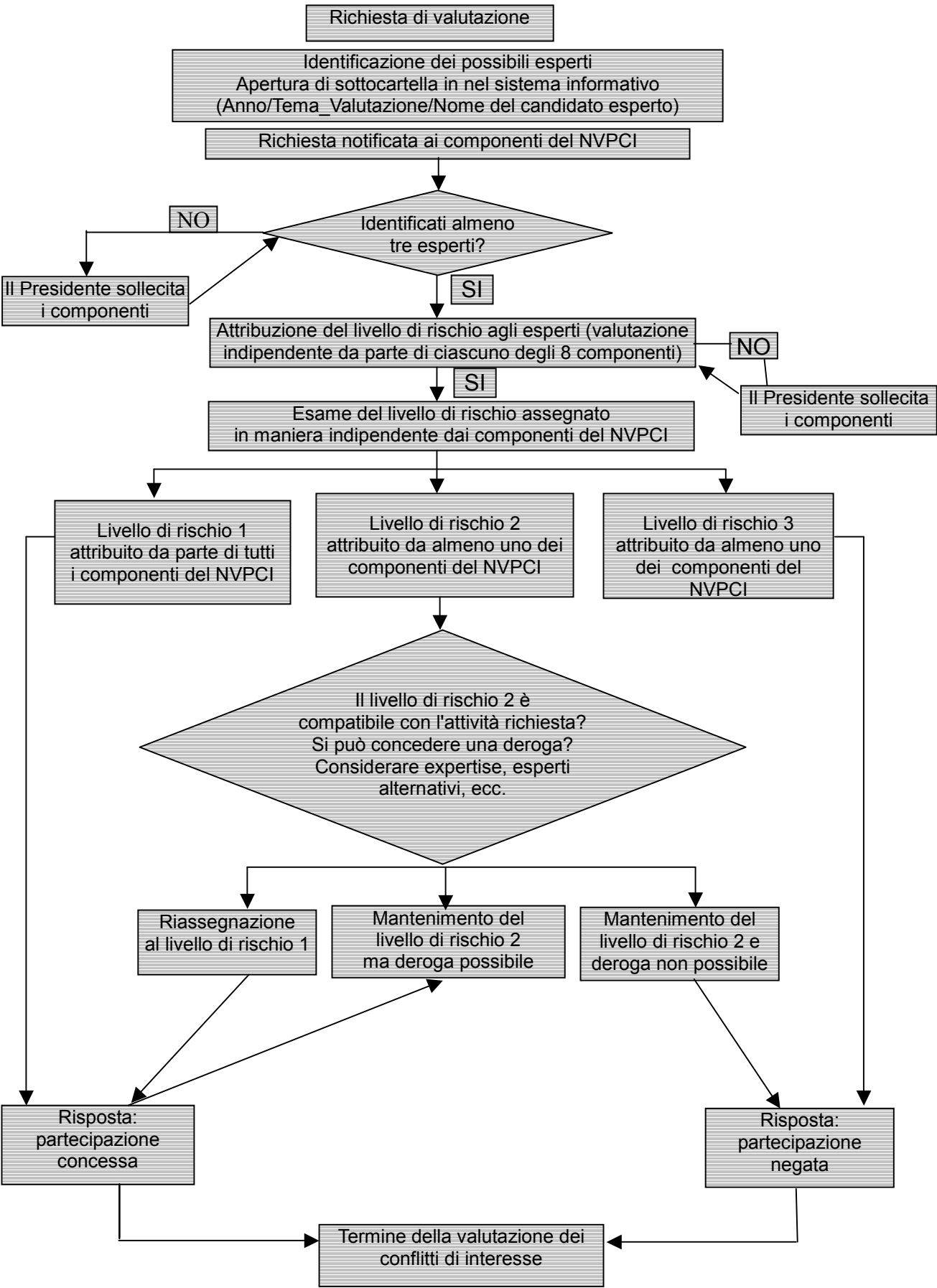
- l'identificazione dei possibili esperti è condotta in modo indipendente da parte di ciascuno dei componenti ordinari del NVPCI e viene condivisa per via *email* all'interno del sistema informativo dedicato: ognuno dei componenti del NVPCI identifica nell'archivio informatico degli esperti accreditati un numero congruo (comunque non inferiore a tre) di professionisti, avendo cura di garantire una bilanciata rappresentazione multiprofessionale e multidisciplinare, e ne comunica infine i dati identificativi al Presidente del NVPCI o ad un suo delegato;
- il Presidente o un suo delegato raccoglie l'elenco dei professionisti identificati dai componenti del NVPCI, lo pubblica nel gestionale di supporto e lo notifica per via *email* ai componenti;
- ognuno dei componenti del NVPCI attribuisce un livello di rischio ad ognuno degli esperti elencati in accordo con la seguente codifica:
 - livello 1: assenza di evidenti conflitti di interesse;
 - livello 2: possibile presenza di conflitti di interesse;
 - livello 3: presenza di conflitti di interesse;
- se il livello di rischio identificato da ciascun componente del NVPCI è di grado 1, questo dato deve essere riportato a cura del Presidente nella risposta del NVPCI (archiviata per via elettronica nell'apposito gestionale) a documentazione della approvazione dell'esperto per la valutazione specifica richiesta, e non è necessaria alcuna valutazione ulteriore;
- se il livello di rischio identificato da uno o più componenti del NVPCI è di grado 3, questo dato deve essere riportato a cura del Presidente nella risposta del NVPCI a documentazione della mancata approvazione dell'esperto per la valutazione specifica richiesta, e non è necessaria alcuna valutazione ulteriore;
- se il livello di rischio identificato da uno o più componenti del NVPCI è di grado 2, il gruppo di valutatori, su sollecitazione del Presidente, effettua un confronto (a distanza per via *email* ed eventualmente tramite incontro) delle valutazioni individuali al fine di ottenere un consenso che può consistere in:
 - derubricazione del livello di rischio al grado 1. In tal caso questo dato viene riportato nella risposta del NVPCI a documentazione della approvazione dell'esperto per la valutazione specifica richiesta, e non è necessaria alcuna valutazione ulteriore;
 - conferma collegiale dell'esistenza di un livello di rischio di grado 2. In tal caso il NVPCI raggiunge ed esprime un consenso motivato circa l'approvazione o la mancata approvazione dell'esperto e riporta tale consenso nella risposta del NVPCI. Tale consenso può assumere la forma di una deroga, assunta sulla base dell'expertise specifica richiesta, della eventuale disponibilità di esperti alternativi con la specifica expertise, della natura della valutazione richiesta e del ruolo dell'esperto o della fase durante la quale ne è richiesto il coinvolgimento;
 - revisione del livello di rischio al grado 3. In tal caso questo dato viene riportato nella risposta del NVPCI a documentazione della mancata approvazione dell'esperto per la valutazione specifica richiesta, e non è necessaria alcuna valutazione ulteriore.

10) Completamento della procedura di valutazione del conflitto di interesse degli esperti

Tutte le decisioni prese dal NVPCI devono essere firmate dal responsabile dell'Unità Operativa Servizi Sanitari Territoriali. La firma deve essere apposta sul modello di valutazione compilato.

Tutte le decisioni (partecipazione concessa/negata; attribuzione del livello di rischio di conflitto di interessi) prese dal NVPCI e confermate dal responsabile dell'Unità Operativa Servizi Sanitari Territoriali sono registrate nella rispettiva sottocartella del sistema informativo dedicato.

Diagramma della procedura di valutazione del conflitto di interesse degli esperti



E. Classification of Documentation of Lombardy VTS-HTA Assessment

CERTAINTY AND ROBUSTNESS DEGREE OF RECOMMENDATIONS

Classification of documentations of comparative effectiveness and of cost-opportunity recommendations:

- **Trial world evidence (TWE)** = normative criteria for reference models (deontological or technological norm)
- **Real world evidence (RWE)** = normality criteria for actual models (distribution of observed behaviors)
- **Evidence and values (EV)** = normative/planning criteria (objectives synthesis, opportunities identification)

Relationship between documentations/recommendations and components of the aid diagnostic-therapeutic pathways (percorsi diagnostico-terapeutici assistenziali – PDTA):

PDTA	Percorso di riferimento	Percorso effettivo	Percorso obiettivo
Documentazione	Trial world evidence ¹⁴⁹	Real world evidence	Evidence and values
Metodo cardine	Randomizzazione	Osservazione naturalistica	Giudizio informato ¹⁵⁰

Classification of documentation/recommendations for each evaluation dimension and for the analysis areas:

Livello 151	Dimensione: Rilevanza generale Area: Descrizione della patologia What is it, how common is it?		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Surveys randomizzate recenti localmente rilevanti (o dati censori)	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Descrizione, gravità malattia - Dimensioni popolazione - Obiettivi sanitari generali - Descrizione tecnologia, aree di beneficio
2	Revisioni sistematiche di surveys recenti	Analisi secondarie degli archivi amministrativi sanitari	
3	Revisioni sistematiche di campioni locali non randomizzati	Audit clinici e serie di casi	
4	Revisioni sistematiche di serie di casi	Riassunti, poster, altri studi ¹⁵²	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

Livello	Dimensione: Rilevanza generale Area: Prognosi What will happen if we do nothing?		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi di coorte dall'esordio (inception cohort studies) ¹⁵³	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Descrizione, gravità malattia - Dimensioni popolazione - Obiettivi sanitari generali - Descrizione tecnologia, aree di beneficio
2	Studi di coorte dall'esordio clinico	Analisi secondarie di archivi amministrativi sanitari	
3	Studi di coorte o bracci di controllo di studi randomizzati	Audit clinici e serie di casi	
4	Revisioni sistematiche di serie di casi	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		
Livello	Dimensione: Efficacia teorica e pratica Area: Screening Is early detection worthwhile?		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi randomizzati	Analisi di registri di patologia,	Giudizi informati su:

¹⁴⁹ Adattato da: OCEBM Table of Evidence Working Group*. "The Oxford 2011 Table of Evidence". Oxford Centre for Evidence Based Medicine. <http://www.cebm.net/index.aspx?o=5653>. * OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson.

¹⁵⁰ **Giudizio informato per criteri espliciti:** pesatura preventiva, attribuzione personale di punteggi su scala ordinata, composizione di un indice di opportunità, raccolta e sintesi di commenti. **Giudizio informato per criteri impliciti:** attribuzione personale di un giudizio qualitativo, raccolta e sintesi di commenti.

¹⁵¹ Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

¹⁵² Compresi dati non ancora pubblicati ed autocertificati di pregresse esperienze applicative sperimentali e/o cliniche.

¹⁵³ *Inception cohort*: a group of patients who are assembled near the onset of the target disorder. Tratto da Bannister.

		Rapporti HTA di altre istituzioni	- Miglioramento <i>efficacy</i> e <i>effectiveness</i> - Esiti riferiti dai pazienti (ERP) - Linee guida, autorizzazioni - Alternative tecnologiche
2	Studi randomizzati	Analisi secondarie di archivi amministrativi sanitari	
3	Studi di coorte o di follow-up controllati non randomizzati	Audit clinici e serie di casi	
4	Studi caso-controllo o con controlli storici	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

Livello	Dimensione: Efficacia teorica e pratica Area: Diagnosi Is this test accurate?		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi di prevalenza ¹⁵⁴ con applicazione coerente di mascheramento e riferimento esterno	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Miglioramento <i>efficacy</i> e <i>effectiveness</i> - Esiti riferiti dai pazienti (ERP) - Linee guida, autorizzazioni - Alternative tecnologiche
2	Revisioni sistematiche di studi di prevalenza	Analisi secondarie di archivi amministrativi sanitari	
3	Revisioni sistematiche di casistiche non controllate, o di studi senza applicazione coerente di riferimento esterno	Audit clinici e serie di casi	
4	Revisioni sistematiche di studi caso-controllo, o studi di prevalenza con uso di riferimento esterno non indipendente	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

Livello	Dimensione: Efficacia teorica e pratica Area: Terapia Does this treatment help? (Treatment benefits)		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi randomizzati oppure studi randomizzati su singolo (n-of-1 trial) ¹⁵⁵	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Miglioramento <i>efficacy</i> e <i>effectiveness</i> - Esiti riferiti dai pazienti (ERP) - Linee guida, autorizzazioni - Alternative tecnologiche
2	Studi randomizzati o (in via eccezionale) studi osservazionali con effetto clamoroso	Analisi secondarie di archivi amministrativi sanitari	
3	Studi di coorte o di follow-up controllati non randomizzati	Audit clinici e serie di casi	
4	Revisioni sistematiche di studi caso-controllo o con controlli storici	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

¹⁵⁴ **Cross-sectional study (prevalence study)** A (prospective or retrospective) observational study in which a group is chosen (sometimes as a random sample) from a certain larger population, and the exposures of people in the group to an intervention and outcomes of interest are determined (tratto da INAHTA HTA Glossary).

¹⁵⁵ **N of 1 trial** A clinical trial in which a single patient is the total population for the trial, including a single case study. Random allocation may be used to determine the order in which an experimental and a control intervention are given. (tratto da INAHTA HTA Glossary).

Livello	Dimensione: Sicurezza Area: Terapia What are the common harms? (Treatment harms)		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi randomizzati oppure studi randomizzati su singolo (<i>n</i> -of-1 trial)	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Miglioramento di sicurezza e tollerabilità
2	Revisioni sistematiche di studi caso controllo nidificati o con effetto clamoroso	Studi di sorveglianza	
3	Studi di coorte o di follow-up controllati non randomizzati	Audit clinici e serie di casi	
4	Studi caso-controllo o con controlli storici	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

Livello	Dimensione: Sicurezza Area: Terapia What are the rare harms? (Treatment harms)		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi caso-controllo o osservazionali con effetto clamoroso	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Miglioramento di sicurezza e tollerabilità
2	Studi randomizzati o (in via eccezionale) studi osservazionali con effetto clamoroso	Studi di sorveglianza	
3	Studi di coorte o di follow-up controllati non randomizzati	Audit clinici e serie di casi	
4	Studi caso-controllo o con controlli storici	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

Livello	Dimensione: Impatto economico e finanziario Area: Sostenibilità finanziaria Is it cost-effective?		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi randomizzati oppure studi randomizzati su singolo (<i>n</i> -of-1 trial)	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Impatto finanziario SSN - Costo-efficacia - Altre spese - Costo-opportunità
2	Studi randomizzati o (in via eccezionale) studi osservazionali con effetto clamoroso	Analisi economiche su dati reali ¹⁵⁶ , Analisi secondarie di archivi amministrativi sanitari	
3	Studi di coorte o di follow-up controllati non randomizzati	Studi di modellistica economica, Audit clinici e serie di casi	
4	Revisioni sistematiche di studi caso-controllo o con controlli storici	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

Livello	Dimensioni: Equità di accesso, impatto sociale ed etico, impatto organizzativo Area: Sostenibilità etica, sociale ed organizzativa Is this treatment equitable, socially accepted, feasible? (ethical, social and organisational sustainability of the treatment)		
	R = Percorso di riferimento	E = Percorso effettivo	O = Percorso obiettivo
1	Revisioni sistematiche di studi randomizzati oppure studi randomizzati su singolo (<i>n</i> -of-1 trial)	Analisi di registri di patologia, Rapporti HTA di altre istituzioni	Giudizi informati su: - Impatto su equità ed accessibilità delle prestazioni - Indirizzi programmatori - Impatto sul bisogno sanitario - Portatori di interesse - Contesto storico-politico - Capacità del sistema ed uso appropriato della tecnologia
2	Studi randomizzati o (in via eccezionale) studi osservazionali con effetto clamoroso	Analisi secondarie di archivi amministrativi sanitari	
3	Studi di coorte o di follow-up controllati non randomizzati	Audit clinici e serie di casi	
4	Revisioni sistematiche di studi caso-controllo o con controlli storici	Riassunti, poster, altri studi	
5	Opinioni senza esplicita analisi critica, esperienze limitate o non pubblicate, analisi fisiopatologiche		

¹⁵⁶ Studi di costo-efficacia, costo-utilità, costo-beneficio, altre tipologie.

F. Interviews: Questions and Answers

Axes of analysis:

1. Importanza e rilevanza delle evidenze disponibili;
2. Paziente: impatto sul coinvolgimento nel trattamento scelto, cambiamento qualità della vita e soddisfazione;
3. Tecnologia: ciclo di vita e stato regolatorio;
4. Economics: conseguenze di disinvestimenti e risparmi per altre operazioni;
5. Sistema organizzativo e contesto politico/pubblico: gestione del cambiamento a livello ospedaliero, implicazioni delle scelte nell'ambito di altre regioni.

Domanda	Risposta (I nomi complete non sono riportati per motivi di privacy)
1. Qual è il suo ruolo professionale?	MS-B Direttore del dipartimento geriatrico cardiovascolare di un ospedale di medie dimensioni.
	LCD'O Medico, epidemiologo, responsabile dell'unità operativa di epidemiologia di Asl.
	MT Medico, con mandato in Regione per la valutazione di tecnologie sanitarie nella direzione generale sanità.
	LC Direttore sanitario di un centro cardiologico di medie dimensioni.
	PB Responsabile della qualità dell'azienda ospedaliera di piccole dimensioni nonché risk manager, in quanto la regione sta promuovendo l'integrazione delle due funzioni. In particolare, si valuta la qualità delle prestazioni e in generale delle attività sanitarie in base a standard condivisi da tutte le altre aziende sanitarie della regione Lombardia, secondo un modello codificato.
2. La decisione finale di appropriatezza può essere basata esclusivamente sulle informazioni raccolte nella SIM? Esistono criticità?	MS-B I criteri indicati nella SIM sono sufficienti per il giudizio finale, in quanto, anche per la valutazione dell'aspetto finale di efficacia e sicurezza, ci si serve di informazioni risultanti sia da evidenza scientifica di trial clinici (se esistenti), sia da dati del mondo reale internazionale come registri e studi osservazionali fatti sul campo della clinica quotidiana, in più di risultati del DWH regionale, che consentono di dare un quadro dell'utilizzo degli interventi in ambito regionale. Gli elementi della SIM sono sufficienti, ma non è possibile inserire alcuni dati, che non sono recuperabili dalla letteratura o comunque in tempi brevi. La valutazione serve anche per dare degli auspici per il futuro, ad esempio la necessità di ulteriori trial clinici, o l'istituzione di registri, attualmente inesistenti, oppure studi di impatto economico, che sono quelli più carenti in generale. La SIM è potenzialmente appropriata in quanto copre tutti gli aspetti di utilizzo delle tecnologie; laddove ci siano gap notevoli, di solito non si inizia nemmeno il procedimento di HTA. Se si passa alla fase di priorità, ciò significa che comunque c'è una base sufficiente per una valutazione finale. I domini della SIM più carenti di informazioni sono: - Economico: cost-effectiveness, costi diretti e indiretti (soprattutto indiretti); gli studi presenti sono solo simulazioni e nei trial si fanno poche valutazioni economiche; - Organizzativo: sul PFO non c'è molto; - Equità, etica, risposta del paziente: su questo non sono a

	disposizione molte informazioni (questo vale anche in generale). I criteri di prevalenza del fenomeno, quelli di efficacia e sicurezza sono normalmente più completi. LCD'O Si, è sufficiente ai fini della decisione per il TTRAM; per questa specifica patologia le informazioni sono sufficienti per prendere una decisione. In questo caso, ad esempio, l'impatto finanziario è by product, cioè le evidenze in termini di indicazioni e di come il panorama sanitario si muove per gestire questi interventi sono talmente chiare che l'impatto finanziario è quasi secondario; a prescindere dai costi, ci sono evidenze di inappropriately molto marcate in termini di che cosa viene fatto, quindi qualunque sia l'impatto finanziario che è implicito nell'utilizzo di questa tecnologia, è quasi superfluo! In questo caso c'è un improprio uso della tecnologia, clinicamente parlando. Inoltre, in termini di equità, vi è l'utilizzo di una metodica di non provata utilità e anzi potenzialmente foriera di pericoli per una popolazione per la quale non è indicato questo tipo di approccio. L'intervento di per sé può esporre teoricamente ad un incremento di rischi di fibrillazione atriale o ictus cerebrali, quindi si rischia di fare un intervento che può essere utile, ma in altri casi anche dannoso e rischioso. MT La decisione sarà basata sulle informazioni raccolte, interpretate dal TTRAM, che dovrà guardare gli elementi contenuti nella SIM e giudicare ogni criterio. Per definizione, lo sforzo di costruzione della SIM potrà essere incompleto per carenza di informazioni, ma i nominati sono tenuti ad esprimere un giudizio personale su tutti i criteri; ovviamente, dove la documentazione sarà scarsa o nulla, il valore del giudizio raccolto sarà minore rispetto a quello dei criteri con più informazioni, ma sarà comunque a giudizio del componente nominato, in quanto la fase di Appraisal è fatta sotto raccolta di giudizi informati. È necessario comunque prendere una decisione, anche provvisoria, in attesa di maggior evidenza scientifica. <i>Nel caso specifico del PFO, la SIM verrà cambiata a valle di nuovi trial randomizzati in uscita?</i> Certamente. Quando i nuovi studi usciranno sarà necessario riprendere mano alla valutazione aggiungendo dettagli alle singole dimensioni, tramite un upgrade del singolo criterio, con un punteggio differente; infatti, nel caso del PFO, almeno tre studi sono in fase di uscita, uno dei quali dovrebbe uscire a novembre. Tuttavia questo vale in linea generale, in quanto non esiste esperienza al riguardo e si è solo alla fase di redazione del rapporto strutturato; anche dopo l'adozione di una decisione regionale sulla base di una valutazione di giudizi informati, sarà possibile riaprire il discorso. Per questa specifica valutazione si potrebbe discutere se attendere l'uscita dei prossimi studi o meno, ma la decisione di completare la valutazione o sospenderla per rimandarla all'anno prossimo sarà del gruppo di esperti: in realtà, i dati disponibili attualmente chiariscono in modo evidente la situazione e non si attendono dei grossi cambiamenti. Una recente analisi di quattro studi negli Stati Uniti, che comprendono anche gli abstract in anteprima degli studi in via di pubblicazione, non ha modificato la pratica. L'analisi epidemiologica della popolazione, dei consumi legati a questa tecnologia e dei primi esiti, nel senso di prevenzione di eventi cerebrovascolari (non si è ancora guardato alla migraine), ha formulato alcune ipotesi che potrebbero essere approfondite in termini di impatti sulla salute, come un outcome based research, o anche di informazioni cliniche raccolte tramite un registro dell'intervento di chiusura del PFO
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	nell'adulto. Infatti l'esito delle valutazioni non riguarda soltanto un contesto appropriato, con un percorso diagnostico terapeutico adeguato per l'avvio dei pazienti alla procedura (identificazione dei pazienti), una restrizione dei centri appropriati per implementare la procedura, oppure una revisione tariffaria per il rimborso del dispositivo, bensì c'è anche la possibilità di indicare delle aree di approfondimento: sarà quindi importante proporre la costruzione di un registro che consenta il tracciamento di tutte le informazioni cliniche dei pazienti a cui è indicato questo intervento, in modo da poter complementare le informazioni di natura sanitaria derivate dal database amministrativo con dei dati più specifici. Ipotizzo che il gruppo di valutatori possa decidere a favore di questo esito, modo che ci sia un beneficio della popolazione. LC Le informazioni comprese nella SIM sono complete, soprattutto per quanto riguarda l'efficacia; tuttavia, potrebbero esserci novità da risultati di trial randomizzati appena discussi durante un convegno la settimana scorsa, che potrebbero cambiare alcune prospettive, in quanto i risultati, non ancora pubblicati, che hanno una latenza di 1-1,5 anni dalla pubblicazione, sono più favorevoli all'efficacia della procedura di chiusura rispetto alla terapia medica. I dati all'interno della SIM sono sufficienti per poter prendere una decisione: in questo caso non si parla di abolire la procedura, bensì di rivedere i pazienti eligibili, quindi i nuovi risultati pongono un nuovo quesito su quando implementare la procedura, cioè se soltanto dopo il primo episodio di recidiva, o direttamente dopo il primo sintomo. Se i nuovi dati abbassassero l'efficacia della terapia medica, allora sarebbe necessario intervenire subito con la chiusura per prevenire il secondo evento di ictus. PB Sì, ci sono informazioni sufficienti per prendere una decisione di appropriatezza. Per quel che riguarda i criteri non computabili, essi possono essere descritti e stimati, non necessariamente quantificati con precisione, ma comunque una stima di impatto può essere effettuata.
3. Quale dovrebbe essere l'esito del processo di valutazione a molti criteri nel caso in cui una o più dimensioni (ad esempio sicurezza e tollerabilità dell'intervento) si rivelassero al di sotto di un determinato livello di accettabilità?	MS-B Il problema del PFO riguarda più che altro l'efficacia; non è necessario fermarsi all'Assessment, infatti il ruolo dell'HTA è proprio quello di far emergere tecnologie che sono diffuse, ma non sufficientemente efficaci. Per quanto riguarda la sicurezza, esistono organizzazioni come il post-market surveillance che verifica, soprattutto per dispositivi impiantabili, notifica e segnala problemi di sicurezza del paziente. Normalmente il vaglio per avere il marchio CE e mettere in commercio il dispositivo in Europa si avvale della dimostrazione di sicurezza. Quando gli studi di sicurezza non sono così ampi da escludere a priori la possibilità di eventi avversi, l'HTA può valutare la non sicurezza di un dispositivo; tuttavia, normalmente il ruolo dell'HTA è quello di valutare l'efficacia e l'appropriatezza d'uso. La valutazione finale non è basata solo su soglie e numeri, in quanto il numero dà indicazioni comparative rispetto ad altri dispositivi; difficilmente un dispositivo che ha punteggio 0 raggiunge la soglia di sufficienza. LCD'O Non è necessario interrompere la fase di Assessment perchè in questi casi frequentemente mancano elementi di queste dimensioni, cioè è necessario adeguarsi alla realtà e alle disponibilità quando ci sono aspetti cogenti che sono sufficienti per esprimere un'opinione; altri aspetti, che sono più marginali, diventano secondari quando esiste una forte evidenza

	di efficacia e che può essere foriera di rischi. La letteratura lascia un margine di indicazioni per quei pazienti con eventi ictali pregressi, quindi sarebbe necessario essere stringenti sul fatto che chi riceve questa tecnologia ricada effettivamente in questa tipologia per la quale non è esclusa una potenziale utilità. MT L'esperienza dell'applicazione dell'MCDA è solo iniziale in Lombardia, ma il programma ha l'assunto di base che la matrice comprende tutte le dimensioni che coprono le varie aree di applicazione della tecnologia in esame, e anche in carenza di documentazione si possa comunque raggiungere un giudizio (ciò soprattutto per i criteri di impatto sociale, etico e organizzativo). I clinici danno comunque per scontata la credibilità della tecnologia, e in carenza di informazioni possono attribuire anche un punteggio neutro. In un caso eccezionale in cui in fase di Assessment si identificano informazioni che raggiungono un livello di allarme su un criterio, questa osservazione dovrebbe portare ad una raccomandazione per la ricerca e per la pratica, e a maggior ragione è importante la registrazione di pazienti e la raccolta di dati. Il caso normale, quindi, è quello in cui la documentazione esistente permetta l'espressione di un giudizio; in alcuni casi questo può essere neutrale, ma la matrice è sufficientemente plastica per rappresentare pesi e punteggi derivati da documentazione robusta per alcuni criteri, e punteggi più discutibili (neutrali) per altri criteri, nel senso che rappresenta l'eterogeneità di qualità della base documentale e di qualità della valutazione generale stessa. Questo tipo analisi comprende l'esame comparativo di attributi decisionali di natura differente, quindi non è il modello analitico che porta alla decisione, al contrario di come può succedere per indicatori monetari. Nel caso eccezionale, invece, si arriva alla fase di Appraisal, ma una delle conclusioni possibili è la generazione di atti per la raccolta di informazioni che possono migliorare il percorso dell'appropriato uso della tecnologia. Il modello matematico è volutamente semplicistico, in quanto determina un numero che corrisponde all'impatto globale della tecnologia. Si è voluto applicare la forma più semplice di questo tipo di modelli, ma in questa prima fase di implementazione del programma si sono preferite attendibilità e generalizzabilità piuttosto che una precisione rispetto ai problemi posti. La misura è certamente affidabile, anche se imprecisa, e consente comunque di prendere una decisione; non si esclude in futuro di utilizzare altri modelli più sofisticati per impatti budgetari molto alti. In letteratura, esperienze internazionali corrispondono all'utilizzo di questo modello, in cui il livello di computo dei parametri è molto semplice per costruire un indicatore univoco, che è complementato dall'inserimento di commenti, che permettono un confronto di coerenza tra il punteggio espresso e il pensiero del valutatore, all'interno del gruppo. I feedback permettono quindi il dialogo e l'identificazione di aree più o meno note per i diversi valutatori, al fine di aumentare il livello di consapevolezza all'interno del gruppo. L'MCDA non si conclude qui, ma si completa con la discussione tra tutti i partecipanti e si concretizza nella stesura di un insieme di motivazioni che costituiscono la sintesi per l'indicazione di appropriatezza d'uso e per la parte clinica. L'MCDA aiuta i valutatori ad avere idee più chiare e ad esprimere meglio i propri giudizi, complementata da una fase di confronto che si concreta in una raccomandazione sintetica di indicazioni. A volte il proprio parere è differente rispetto a quello del gruppo, perciò è importante il confronto e la discussione aperta in modo da raggiungere un'approvazione ragionata e motivata.
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	LC In generale, è necessario proseguire fino all'ultima fase della valutazione, ma esistono casi particolari in cui emergono evidenze di rischio. Sulle metodiche esistono 3 livelli di risultati: semaforo verde, per cui il trattamento o l'utilizzo del device è positivo per il paziente, cioè ci sono più vantaggi e scarsi o nulli rischi, semaforo giallo per cui risultati positivi e negativi vengono bilanciati, semaforo rosso, per cui i rischi sono molto probabili e i vantaggi nulli. Per i semafori verde e giallo, si potrebbe proseguire al TTRAM, mentre per il rosso ci si ferma prima. I risultati della metodica vanno poi incrociati nella matrice con i risultati di evidenza clinica. PB La valutazione deve comunque arrivare alla fine e indicare i casi in cui la procedura non è utilizzabile o è riservata solo per alcuni pazienti. Per quanto riguarda lo specifico indicatore MCDA, in futuro, in base all'esperienza fatta, potrà essere necessario avere un approccio più strutturato rispetto a quello attuale, mentre in questo momento si può arrivare a decisioni dando giudizi che non richiedono un approccio così strutturato dal punto di vista della misurazione delle dimensioni.
4.1 Quali potrebbero essere le conseguenze nel processo di valutazione se pazienti/associazioni vengono coinvolte?	MS-B Pazienti o associazioni possono essere coinvolti, ma solo ad hoc, cioè non è utile averli come partecipanti del TTRAM, bensì potrebbero essere coinvolti nel tavolo di Assessment, allo stesso modo degli esperti di settore; non li vedrei come componenti di Nucleo e Tavolo, ma possono partecipare a seconda del tipo di valutazione. LCD'O Concretamente il coinvolgimento è fattibile a patto che ci sia una selezione di rappresentanti di associazioni di pazienti in grado di interloquire su una base tecnica rispetto alle posizioni prese dal Nucleo. Se le associazioni di pazienti propongono esperti, essi possono essere coinvolti anche in fase iniziale. Sicuramente potrebbero entrare in fase di Priorità, e verosimilmente anche nelle altre, ma con un ruolo di intervento valido, e non soltanto come interessati ad un potenziale beneficio. Esempio: alcune associazioni di pazienti in ambito dermatologico sono quasi più esigenti dei tecnici stessi nel voler avere prove di evidenza di efficacia, altre invece perorano la causa di una speranza "indefinita" che ci sia il beneficio. Se si interloquisce con rappresentanti di associazioni di pazienti che parlano lo stesso linguaggio e possono entrare nel merito delle singole dimensioni su base ragionevole, possono partecipare in qualunque fase del processo; se invece sono rappresentanti di "speranze indefinite" di beneficio, ma non suffragate da evidenza, allora costituiscono più un disturbo. MT L'esperienza è ancora limitata, in quanto è capitato un caso, ma solo nell'ambito di piccole reti di patologia. Tuttavia ci si sta preparando, anche se si sa dalla letteratura che ciò potrebbe essere sia complicante che facilitante per un programma di valutazione: facilitante nel momento in cui le associazioni di cittadini sono preparate; la Regione si sta infatti chiedendo non quale sia il livello di expertise in termini tecnici, quanto più quello in termini più generici e valutativi di rappresentanza per il coinvolgimento di pazienti. Essi possono essere accettati se posseggono il linguaggio, sono preparati e formati adeguatamente, in modo da portare un contributo critico, ma comunque comprensibile. Le associazioni possono essere ostative nel momento in cui il gruppo di pazienti è così interessato alla tecnologia, o per pressione o spinta politica, che, anche in assenza di documentazione che ne consigli l'uso, spinge sulla regione o

	sull'ente amministrativo per ottenere l'adozione della tecnologia indipendentemente da quello che viene acclarato. Ciò è difficile da governare, in quanto in Italia è successo che pazienti con scarse alternative terapeutiche sono stati spesso indotti da una pressione mediatica e da una dichiarazione dei ricercatori, in modo da ottenere disponibilità di queste terapie che si rivelano poi essere non supportate da documentazione scientifica. I rappresentanti devono quindi essere filtrati nell'inserimento, in modo che lo scambio di conoscenze sia credibile e fornisca positivamente contributi e documentazioni anche della loro esperienza sul campo. Per coinvolgere associazioni di cittadini in regione è necessario un bando pubblico per la raccolta di disponibilità di associazioni sul campo nazionale, ma questo processo può essere allungato dalla questione della attuale vacanza della giunta regionale. La delibera attualmente non prevede il coinvolgimento di pazienti, quindi saranno necessari sia un intervento regolatorio, sia delle prove con alcune valutazioni e, quindi, una delibera che tenga conto di queste informazioni raccolte. In questo senso, in linea generale la fase di Priorità è talmente tecnica e complessa (e spesso le informazioni sono molto scarse) che il punto di vista di associazioni di cittadini può non essere ricercato, in quanto comunque si giunge ad una discussione tecnica sufficientemente valida per passare alla seconda fase. Nelle fasi di Assessment e Appraisal è importante avere un contributo, ma differenziato: nella prima ha senso coinvolgere associazioni di pazienti e volontari, purché robuste e rappresentative, non portatrici di interessi di professionisti che le strumentalizzano, in modo che esprimano un parere sulla loro esperienza, e discutano anche riguardo a tutti i criteri della matrice. In fase di Appraisal, invece, è meglio prevedere un ruolo per associazioni di cittadini, e non di pazienti, che abbiano un certo distacco rispetto alla malattia. In fase di giudizio, è importante che i rappresentanti di cittadini, opportunamente selezionati, al pari livello dei nominati, possano esprimere in libertà un giudizio informato mantenendo un punto di vista sociale, essendo corresponsabili della decisione finale. LC I pazienti possono essere coinvolti nella fase finale, in quanto non dispongono di altri strumenti altrove. Chiaramente, vanno coinvolte persone qualificate, in quanto portatori di interesse. PB I pazienti dovrebbero essere coinvolti nella fase di Appraisal, in modo da esprimere un giudizio diretto.
4.2 Gli esiti riferiti dai pazienti potrebbero portare una differente decisione di appropriatezza dell'intervento o cambiare la sua attendibilità?	MS-B Sul PFO non ha molto senso coinvolgere pazienti. Ciò può valere su dispositivi o trattamenti farmacologici controversi, o in campi in cui c'è molto poco sull'efficacia, e quindi c'è spinta a capire quanto un determinato intervento ha impatto sulla qualità della vita. Ad esempio, su farmaci per il cancro o interventi per la sclerosi multipla, come l'angioplastica venosa, il parere del paziente o una sua associazione va ascoltato. Il loro coinvolgimento non è per prendere necessariamente una posizione totalmente favorevole o per accontentare tutte le associazioni, ma affinché si raggiunga un bilanciamento sostenibile. L'aspetto più importante è che le persone da ascoltare vengano selezionate attentamente e siano accreditate. È necessario evitare scarsa serietà o conflitti di interesse derivanti da aziende che possono stare dietro i pazienti. LCD'O Secondo me non dovrebbe esserci un impatto in termini di esiti riferiti dai

	pazienti, in quanto in questa tecnologia l'esito avverso sarebbe molto drammatico, a tal punto che il paziente non può più interloquire; se invece il paziente si dice più "tranquillo" a fronte dell'intervento, ciò risulta influente in assenza di evidenza che la sua mancata recidiva di ictus possa veramente essere legata all'intervento sostenuto. Per il PFO il parere dei soggetti che hanno avuto applicata questa tecnologia non è influente in quanto, se non si presenta più un ictus non si è sicuri che sia legato all'intervento, se invece si verifica, potrebbe essere paradossalmente legato all'intervento stesso e, di solito, chi successivamente ha un problema importante, non è più in grado di riportare la propria esperienza.
	MT Sul PFO non sono state ancora coinvolte persone, ma, essendo un caso di nicchia, non credo siano nate negli anni passati associazioni che si occupino solo di questa patologia. In realtà, ciò che potrebbe essere interessante esaminare per questi pazienti è il percorso dell'ictus criptogenetico e della cefalea cronica non risolta con altre soluzioni, anche se in queste aree la ricerca scientifica non è molto sviluppata. Il gruppo di lavoro non ha al momento segnalato alcuna associazione. Nel mio parere, è già sufficiente ciò che emerge dagli studi clinici controllati per prendere una decisione sulla revisione della tariffa e dei centri accreditabili.
	LC Il punto è importante, in quanto è necessario considerare i casi specifici delle persone per la scelta della terapia. Per questo motivo è necessaria una rappresentanza, ma che sia ben informata.
	PB Nel caso del PFO, essendoci informazioni che riguardano un determinato livello di efficacia, gli esiti riferiti dai pazienti sono pressoché irrilevanti, in quanto il giudizio professionale che è a monte ha maggior peso. In teoria, i pesi del giudizio professionale e dei pazienti dovrebbero essere gli stessi, ma in questo caso, essendoci preoccupazioni per la sicurezza e l'efficacia del trattamento, il giudizio professionale ha peso maggiore.
4.3 Le informazioni riguardanti qualità della vita/soddisfazione/recidiva hanno un impatto sulle scelte di disinvestimento?	MS-B Un impatto esiste, ma non ci si può far trascinare da queste associazioni che avanzano pressioni.
	LCD'O In assenza di evidenze di efficacia, il peso delle informazioni riguardanti la qualità della vita è molto marginale. L'evidenza può essere fornita esclusivamente da trial randomizzati o da studi di outcome con un numero sufficientemente alto in termini di effectiveness della procedura in modo da escludere rischi di prendere "lucciole per lanterne". È utile considerare l'esito del paziente nel caso ci sia evidenza di efficacia della procedura o del farmaco. NB: questa risposta può essere affetta da "BIAS EPIDEMIOLOGICO", a detta dell'intervistato stesso!
	MT Vedi precedente risposta
	LC A parità di efficacia dei trattamenti, è necessario considerare la qualità della vita: da una parte, con la procedura, anche se può esserci paura dell'intervento, il problema è risolto per tutta la vita, dall'altra invece si assume un farmaco a vita.
5.1 La tecnologia è al suo livello di maturità o potrebbero esserci	PB Non c'è un grande impatto sulla scelta, dal momento che è più importante ciò che emerge dall'evidenza scientifica.
	MS-B C'è stata un'evoluzione, tanto è vero che il dispositivo utilizzato nell'unico

evoluzioni tecnologiche? Quali sono gli outcomes attesi?	trial clinico non viene più utilizzato, e sono emersi nuovi modelli di device. Fortunatamente esistono trial clinici in corso, e si spera che i nuovi dispositivi siano più sicuri ed efficaci. La fase del ciclo di vita della tecnologia non è ancora quella di maturità, bensì quella di evoluzione/crescita.
	LCD'O La tecnologia è in fase abbastanza evoluta, ma non so se stia uscendo qualcosa di più nuovo.
	MT La tecnologia è già oltre la fase di introduzione e diffusione, cioè è prossima ad una fase di maturità, dal momento che c'è stato un avanzamento durante gli anni, ma senza grandi stravolgimenti strutturali della tecnologia. Si è perciò prossimi ad un plateau per la tecnologia consolidata. Il vero problema è che, nonostante la tecnologia sia consolidata, il quesito clinico è discutibile, cioè l'impatto in termini di salute non è mai stato verificato essere positivo, o comunque esistente, se non da pochi centri con grandi esperienze numeriche, che soggettivamente hanno ritenuto opportuno eseguire la procedura, in quanto ritenuta funzionante. Una prova che la tecnologia prevenga l'ictus e modifichi la cefalea non è mai stata raggiunta da alcuno studio clinico controllato e dalle informazioni disponibili. Ciò significa che la tecnologia è stata più veloce a maturare della domanda clinica : in questo senso, l'impatto di una revisione delle indicazioni provocherà per gli ospedali una ricalibrazione dei centri, una revisione della tariffa di rimborso e dei criteri di selezione dei pazienti decisamente più restrittivi. In questo modo gli ospedali saranno più incentivati ad essere molto attenti nella presa in carico dei pazienti, identificando i casi che massimizzano l'utilizzo della procedura e il suo beneficio.
	LC La tecnologia è ad un buon livello di sviluppo ed è consolidata da anni, anche se si è evoluta dalle prime esperienze. Più che altro si parla di formazione dell'equipe, in quanto prima si faceva l'ecocardiografia transesofagea, mentre ora si implementa l'IVUS (intravascular ultra sound), che abbrevia il procedimento di posizionamento dell'ombrellino attraverso cateteri intravascolari.
	PB L'evoluzione della tecnologia, che è in fase di maturità, è comunque irrilevante rispetto all'appropriatezza del trattamento.
5.2 Nel caso di disinvestimento, quale sarà l'impatto per i produttori di dispositivi e i rapporti di fornitura con gli ospedali?	MS-B Gli ospedali utilizzano dispositivi in commercio, che vengono man mano rinnovati. Se si riducesse il rimborso, potrebbero verificarsi problemi di utilizzo. Non si vuole arrivare a ridurre o eliminare la possibilità di utilizzo di questi dispositivi, ma di limitarne l'uso ai casi appropriati, cioè in questo momento ne vengono impiantati troppi, anche a persone che non ne hanno reale bisogno, e quindi l'obiettivo è di rimborsare la quota adeguata per il dispositivo a coloro che vengono appropriatamente operati. Il problema infatti è di porre a rischio i pazienti senza reale beneficio.
	LCD'O (Domanda non posta perché non specializzato sulla tecnologia.)
	MT Certamente per i produttori questa decisione può avere un impatto in termini negativi di profitto, perciò potranno esserci produttori interessati a completare studi post-registrativi, maggiormente informativi rispetto a quelli attualmente disponibili. Si prevede che i produttori si impegneranno

	maggiormente nell'accelerare informazioni credibili e coerenti per l'impatto reale dell'intervento di chiusura. Un impatto immediato può essere espresso tramite l'appello, che permette alle aziende produttrici di esprimersi contro una riduzione delle procedure. Come dimostrano i risultati lombardi dell'ultimo decennio, la tecnologia è stata usata con "presunzione" di efficacia, ma nessuno sa se effettivamente sia efficace.
	LC In linea di massima, dai risultati dell'analisi delle SDO è emerso un 50% di casi inappropriati, quindi anche per i produttori ci sarà una riduzione della possibilità di vendita per un'applicazione più efficace del trattamento.
	PB Sicuramente ci sarà una contrazione della domanda, e ciò impatterà sulle perdite dei produttori.
6.1 Quali potrebbero essere le conseguenze di disinvestimento e quali i costi futuri per ospedali, Asl e SSR? In quale percentuale gli interventi attualmente attuati dovrebbero essere ridotti?	MS-B Un rigido controllo delle procedure porterebbero risparmi e conseguenze a livello organizzativo; questi ospedali faranno attività alternative, oppure saranno costretti a cambiare l'organizzazione. In Lombardia ci sono troppe sale emodinamiche (in cui viene fatta l'operazione), ed esiste già un'iniziativa, in particolare nella città di Milano, a ridurre drasticamente la presenza, cioè 7-8 emodinamiche su un totale di 20. Tutte quelle con un volume troppo piccolo devono essere accorpate in modo da generare un risparmio. Questo approccio non vale solo per il PFO, che è solo una piccola parte della questione, ma soprattutto per gli stent, o gli interventi coronarici (il PFO è solo una nicchia di questi interventi.)
	LCD'O Il risparmio sarebbe notevole, in quanto ci potrebbe essere una riduzione di 2/3 o forse anche di più del numero di interventi totali -> 1/3 o meno restano quelli appropriati.
	MT In questo caso specifico, se l'intervento per l'indicazione di ictus criptogenetico recidivante di prima diagnosi e recidivante è scarsamente documentato, probabilmente ci sarà una contrazione dei casi, in quanto solo dopo il secondo ictus si potrà iniziare a tenere in considerazione l'indicazione e probabilmente il numero di pazienti sarà ristretto. L'impatto sarà una riduzione delle procedure effettuate, ci sarà una riduzione della tariffa per l'intenzione di orientare l'utilizzo in modo più appropriato. Per la Regione sarà un risparmio netto per questo tipo di operazione, mentre per gli ospedali ci sarà una riduzione di quelli che la praticano, con una spinta ad essere selettivi nell'offerta tecnologica. È possibile che il risparmio globale generato permetta il reinvestimento in altre aree simili e di patologia comparabile, ma con più documentazione, oppure per l'istituzione di registri che permettano una migliore interpretazione del valore di appropriatezza d'uso. Una scarsa credibilità e impatto clinico dell'intervento possono essere facilmente reindirizzati in aree di maggior appropriatezza, in quanto il programma regionale tiene sotto controllo diverse linee di intervento. In realtà ciò accade solo tentativamente nello stato economico attuale, tramite l'atteggiamento di spending review: in questo ambito sanitario regionale, ci si trova però di fronte ad un taglio lineare e generalizzato, con richiesta di minori prezzi e di ricontrattazione dei volumi, ma questo non è quindi contesto favorevole per le valutazioni di tecnologie sanitarie, che non devono posizionarsi come strumento di taglio e basta, bensì si segue un concetto di costo opportunità nella stessa area.

	Gli interventi verranno ridotti della metà, o forse anche di più, ma certamente in modo graduale, affinché la classe clinica si adegui, e il numero di casi appropriati in cui è possibile che la tecnologia porti beneficio aumenterà, ma solo in alcuni sottoinsiemi specifici. LC Dai dati disponibili, la riduzione è del 50%, e l'impatto maggiore sarà per le case produttrici piuttosto che per gli ospedali. Sarà più che altro necessario concentrare le procedure in certi centri, mentre le strutture più piccole non devono più implementare la procedura: tuttavia, in questo caso l'impatto degli interventi di questa tipologia è marginale, in quanto i pazienti all'anno non sono tanti. L'inappropriatezza degli interventi registrati deve essere dovuta a coloro che sono stati operati per cefalea o perché sommozzatori professionisti, non essendosi verificato nemmeno il primo evento. Nel restante 50% dei casi, invece, è necessario decidere per la chiusura come prima terapia, oppure quando si verifica una prima recidiva. PB Molti ospedali, che hanno investito molto su questa procedura, sono destinati a dover rivedere il proprio approccio. C'era già un certo livello di inappropriatezza prima che emergessero le evidenze scientifiche, che dimostrano che questa procedura non porta vantaggi nella maggior parte dei casi; è probabile che i medici hanno iniziato indiscriminatamente a svolgere questa procedura in quanto facile e remunerativa. Asl e SSR hanno "tutto da guadagnare" da questa valutazione, mentre alcuni ospedali (non tutti) possono avere un impatto notevole, in quanto almeno il 50% delle procedure sono state inappropriate.
6.2 A valle di una scelta di disinvestimento, come cambiano i costi legati alla gestione del paziente (complicazioni, trattamenti alternativi)? E' meglio la prevenzione o la cura? Qual è il costo dell'intervento confrontato con il costo della terapia medica?	MS-B La terapia alternativa è l'aspirina, che costa pochissimo, quindi dal punto di vista dei costi ci sarebbe un notevole risparmio rispetto all'intervento, per la cui normale l'ospedalizzazione è prevista in 3 giorni. I dati sull'incidenza annuale dei tipi di ictus in Lombardia (forniti nella presentazione ppt) sono una stima approssimativa a titolo esemplificativo. Il calcolo sugli appropriati è basato su un'analisi preliminare di Cavalieri sul 2011 che è stata superata dall'analisi più precisa presentata da Barbieri. In quest'ultima analisi ci sono dati più precisi su PFO e precedente ictus con un tentativo di calcolo di ictus criptogenetico. I pazienti oltre i 18 anni che sono stati sottoposti a chiusura PFO e non hanno avuto neanche un ictus in precedenza dovrebbero essere considerati sicuramente inappropriati. In realtà anche quelli che hanno avuto ictus ma in cui ci sono altre potenziali cause (ad esempio stenosi carotidee, FA) sarebbero da considerare inappropriati. Inoltre, dal momento che l'indicazione della chiusura in alternativa ai farmaci andrebbe riservata o alle recidive in terapia farmacologica o ai pazienti a rischio elevato (ad esempio TVP – trombosi venosa profonda – o disturbi di coagulazione) in cui è controindicata la terapia anticoagulante, il numero degli inappropriati è probabilmente più elevato ma non facilmente quantificabile. LCD'O I farmaci per coloro che non hanno controindicazioni costano molto poco, quindi non ci sono problemi di costi della terapia farmacologica nei soggetti che possono riceverla, in confronto con il costo della terapia chirurgica; in assenza di evidenze di efficacia, non è possibile fare un discorso di trade-off se la terapia farmacologica presenti rischi che la procedura di chiusura sconsigli; purtroppo, la terapia chirurgica espone ad altri tipi di rischi o agli stessi nell'ottica di una mancata soddisfacente risoluzione del problema; se l'ipotesi è che chi sia in terapia farmacologica sia esposto ad un rischio di ictus e continua ad esserne esposto, in realtà

	anche chi segue la terapia chirurgica continua ad esserne esposto, e, paradossalmente, in modo maggiore a causa delle conseguenze dell'intervento. Le emorragie in terapia farmacologica hanno basse percentuali. Riguardo ad un confronto di costi, nel lungo termine non sono sicuramente comparabili. I costi della procedura si aggirano intorno ai 5.000 € + la protesi (3.000€) = 8.000 € circa. MT A fronte di un costo diretto della terapia farmacologica non significativo, si ha un costo molto significativo dell'intervento e il numero di ricoveri per ictus successivi non cambia nella popolazione. Quindi non si può immaginare un costo-efficacia vero e proprio, in quanto questo intervento non cambia il percorso della storia naturale del paziente. La valutazione è molto particolare, in quanto normalmente si prendono decisioni su interventi che cambiano la storia naturale del paziente, ma in questo caso non succede. Non ci si aspetta che questo profondo disinvestimento provochi come conseguenza un incremento di costi dovuti ad un maggior numero di ricoveri per la mancanza dell'intervento; l'intervento è documentato non modificare la storia naturale del paziente, perciò è questionabile l'indicazione dell'intervento stesso. Il costo dell'intervento può cambiare a seconda del tipo di device e della diagnostica implementata (percorso diagnostico-terapeutico e monitoraggio successivo prevedono alcuni esami che hanno un certo costo), quindi 10.000 € è un costo cautelativo (in realtà è maggiore). Una stima di questo costo è al momento secondaria, in quanto per questa valutazione non si è partiti dal dire "è prioritario perché possiamo risparmiare": in questo caso si avrebbe un'idea chiara della stima e ci si farebbe una valutazione, il che sarebbe scorretto. Al contrario, in questo caso alcuni cardiologi hanno segnalato alla regione che in alcuni casi l'intervento portava complicanze significative, tali da dover richiedere spese per i ricoveri e disagi per i pazienti, anche molto significativi, per fortuna infrequenti; a fronte di un'efficacia questionabile, la regione ha deciso di rivedere questo caso, dal momento che un disinvestimento non danneggerebbe il cittadino, dato che una maggiore efficacia non c'è. Quindi non si è partiti da un obiettivo di risparmio, bensì da un obiettivo di appropriatezza clinica, che in questo caso si sposa con un significativo risparmio, che è comunque emerso negli ultimi mesi. La valutazione è strana in quanto la tecnologia si è diffusa velocemente, in carenza di una documentazione e un verificato impatto clinico, ma non è corretto che il pubblico paghi ciò che è creduto funzionante, ma non è dimostrato. Se l'esito della dimostrazione sarà negativo, è verosimile che la tariffa sarà particolarmente svantaggiosa, e comunque ci saranno interventi di dissuasione forte per la presa in carico di questi pazienti. LC In questo caso non c'è un impatto sui centri che fanno l'inserzione dell'ombrellino, in quanto tendenzialmente si tratta di cardiologie interventive o radiologie, e il paziente che ha un ictus non va in cardiologia, ma in ospedale neurologico. I volumi di questa tipologia di ictus non sono elevati; ciò che cambia è a livello di società, nel senso che prevenire o meno un ictus ha un costo notevole dal punto di vista della società per una persona che ha questa tipologia di problemi, nel senso che ha poi bisogno di assistenza e riabilitazione in caso di recidiva. Il confronto tra le terapie può essere quantificato in 15.000 € per un intervento e 20€ per una settimana di terapia anticoagulante, ma la possibilità di prevenire la recidiva impatta molto di più sulla vita del
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	paziente stesso. PB Il trattamento medico ha un costo aggiuntivo pari a zero, nel senso che quei pazienti avrebbero comunque dovuto assumere un trattamento medico dopo l'intervento di inserzione dell'ombrellino. Per quanto riguarda i costi totali, la protesi ad ombrellino si aggira intorno ai 4.000-5.000 €, poi il costo del DRG è di simile ammontare, inteso come rimborso per il ricovero.
7.1 Come cambia l'impatto per quegli ospedali interessati ad implementare l'intervento di chiusura del PFO? Ritiene necessaria una regolazione a livello regionale per l'accreditamento dei centri? Potrebbero verificarsi sovraccarichi per le strutture e il personale coinvolto?	MS-B Questo intervento di accorpamento è necessario in generale, non soltanto per il PFO. Esistono tuttavia alcuni ospedali che fanno tantissimi interventi di PFO: accorpando in certe strutture questa tipologia di interventi, queste ultime potranno dedicarsi solamente a queste attività. È necessario quindi un determinato procedimento di autorizzazioni, che consentirebbero un maggior controllo dell'appropriatezza delle procedure. Quali criteri sono necessari per l'accreditamento? Un numero minimo di procedure eseguite; a differenza di altre operazioni, come ad esempio la TAVI, che sono più complesse, qui la procedura non è complessa e non è di emergenza, quindi ci si basa sul volume passato di attività. LCD'O Si verificherà un cambiamento in termini di indicazioni per l'effettuazione, quindi una riduzione complessiva del volume di attività. I principali erogatori di questa procedura (7 ospedali) raccolgono la maggior parte della casistica e molti di questi con volume più elevato sono strutture private che hanno una tradizione di rinomanza in questo ambito o si sono specializzate in questi interventi, quindi la problematica sarà quella di ripensare al loro modo di saturare le sale operatorie nell'ottica che un privato ha di dover ottenere una quadratura dei conti. Non solo per questa procedura, ma succede che la disponibilità di un margine per singolo intervento abbastanza rilevante di guadagno fa sì che le strutture soprattutto private (ma non esclusivamente quelle private) ritengano particolarmente appetibile il dedicarsi alla selezione dei soggetti in questo ambito. Dovrebbero essere tenuti presenti alcuni parametri per l'accreditamento in termini più generici di volume di procedure per alcuni interventi, ma sicuramente dell'appropriatezza di effettuazione delle indicazioni per altri. L'indagine da parte del medico di verifica del PFO può essere libera, e la decisione della scelta della terapia deve essere in conformità non con indicazioni regionali, ma con le indicazioni della letteratura scientifica sull'argomento. Se, sulla base di queste, la regione si esprime in termini di indicazioni cogenti per la rimborsabilità dell'intervento, il chirurgo deve a maggior ragione adeguarsi, non solo per le evidenze scientifiche, ma anche per le indicazioni regionali. Non in questo caso, ma esistono evidenze che, per certe procedure chirurgiche, il volume rappresenta un fattore indispensabile per fare ciò che gli americani chiamano "practice makes perfect": sotto una certa soglia di procedure svolte la struttura ospedaliera, a prescindere dalla bravura del singolo chirurgo clinico, non è adeguata a gestire il paziente nel suo insieme. Questo è un argomento che, in questa fattispecie, c'entra limitatamente perché di per sé l'intervento non è difficilissimo, quindi non serve una struttura di frontiera per effettuare questo intervento; sicuramente, tuttavia, il rispetto delle indicazioni cliniche, tutte le volte che si decide che il paziente ha le indicazioni per effettuare questo tipo di intervento, deve essere indispensabile dal punto di vista di un

	professionista che propone questo tipo di soluzione.
	MT È necessario che quei centri scelti, dovendo rispondere ad un percorso diagnostico-terapeutico, documentino che tipo di attrezzatura hanno a disposizione e come seguono i pazienti; credo sia importante la registrazione di tutti i singoli pazienti in un registro regionale clinico dettagliato che consenta di verificare nella pratica come stanno andando questi pazienti; in questo senso, l'accreditamento specifico è il primo passaggio per la selezione dei centri e per la costruzione di un registro. I centri a basso volume devono smettere di implementare la procedura, quelli ad alto volume devono ridurre il numero e fare in modo che tutti i loro pazienti arruolati vengano inseriti in un registro. La regione quindi indicherà quali sono i centri autorizzati e i restanti non potranno più implementare l'intervento. Questa logica può sembrare fastidiosa per l'offerta, ma è necessario adeguarsi. I criteri per l'accreditamento, oltre al volume di interventi già eseguiti, saranno quelli indicati in un futuro registro e riguarderanno parametri di sala, diagnostici, di intervento e di follow up.
	LC La necessità di concentrazione dei centri è certa, nel senso che si sa che i risultati sono buoni se si raggiungono dei volumi adeguati; ciò che va fatto è concentrare tutto nei centri a maggior competenza sia tecnica, che nella scelta dei pazienti, quindi di appropriatezza. Chi ha volumi elevati, per quanto riguarda la metodica, va mantenuto, mentre chi ha volumi bassi va escluso.
	PB Tra gli ospedali pubblici esistono coloro che eseguono un certo numero di procedure, i quali ridurranno il numero di indicazioni, ma manterranno la possibilità di eseguire le procedure data l'esperienza. Alcune strutture pubbliche che, al contrario fanno interventi episodicamente (3-4 procedure/anno) vanno tagliate per una questione di sicurezza del paziente, in termini di clinical competence dell'operatore, che deve avere un certo numero di attività. Gli ospedali privati che ricorrono a questa procedura con un elevato grado di inappropriatezza sono anche estremamente rapidi a disinvestire e reinvestire in altre procedure. In totale, gli ospedali in Lombardia che fanno questa procedura sono 30-40, quindi la riduzione porterebbe a 7 ospedali, di cui 2 privati e 5 pubblici. I criteri per l'accreditamento dei centri riguardano non soltanto il numero di procedure già eseguite, ma anche la presenza di una cardiochirurgia, in quanto quelle strutture che, oltre ad una sala emodinamica, hanno anche una cardiochirurgia, hanno emodinamisti più competenti, che sanno gestire anche condizioni di emergenza o particolarmente complesse che richiedano l'intervento cardiocirurgico (come nel caso di rimozione della protesi, che non si è ancorata al tessuto). Gli emodinamisti che lavorano in ospedali senza cardiochirurgia sono molto più orientati sulla singola procedura, e quindi potrebbero non avere competenze in casi di emergenza. Dai risultati dei prossimi trial non ci si attende un cambiamento di quadro rispetto a CLOSURE I in termini di appropriatezza; tuttavia, nel caso ci fossero risultati diversi, che al contrario confermano la maggiore efficacia della chiusura, l'unica cosa da fare è agire sui centri a basso volume, in modo che non implementino più la procedura. Inoltre, a questo punto, i clinici dovranno scrivere un documento di consenso (position paper) in modo da dare indicazioni precise.

7.2 Quali potrebbero essere le implicazioni a livello di comunicazione con le altre regioni?	MS-B Il ridurre il numero di procedure, se fatto in modo appropriato, si riflette anche sulle procedure inappropriate provenienti da altre regioni, quindi gli appropriati in altre regioni potranno continuare a proporsi. Se non viene fatto un filtro dalla regione di provenienza, questo avverrà nella regione di destinazione riguardo all'appropriatezza di un certo intervento.
	LCD'O A livello di benchmarking regionale, la scelta motivata e validamente supportata da evidenze scientifiche di una posizione esplicita contro un abuso di utilizzo di procedure potrebbe avere delle conseguenze. Sicuramente la mobilità sanitaria potrebbe cambiare una volta ristrette le indicazioni. Un altro argomento riguarda il problema etico di effettuare questo intervento anche privatamente solo per preferenza del paziente o per convinzione su basi soggettive dell'efficacia. In ogni modo, la collettività non deve essere esposta al rimborso di una procedura senza una sufficiente validazione di efficacia. Solo la Lombardia ha un certo modello di gestione del privato nell'ambito del servizio sanitario regionale, ma anche altre regioni hanno strutture deputate a fare questo tipo di valutazioni. La legge 31, che è una peculiarità lombarda, prevede la scissione tra Asl e strutture erogatrici con una referenzialità delle strutture territoriali per una valutazione di appropriatezza esterna all'ospedale; nelle altre regioni, invece, gli ospedali pubblici sono ancora a gestione interna nel sistema delle Asl. Sicuramente ci sono peculiarità lombarde, ma una presa di posizione chiara ed esplicita in questo ambito potrebbe fare da traino per ulteriori decisioni che dovrebbero non solo basarsi sul fatto che "la Lombardia lo fa", ma anche dovrebbero evidenziare una consonanza di valutazioni su questo argomento.
	MT L'impatto potrebbe essere significativo in quanto, se la regione è attrezzata e copre un terzo delle indicazioni italiane, è verosimile che altre regioni, che hanno una numerosità inferiore ed esperienze più limitate, adotteranno delle indicazioni simili. La valutazione regionale lombarda potrà essere presa come riferimento per i comitati delle singole regioni, per le quali esiste un'offerta di questo tipo. Ciò è dovuto alla forte attrazione della regione, anche da altre aree.
	LC Dovrebbe comunque esserci un collegamento centrale, tramite il RIHTA ad esempio, in modo da non replicare inutilmente da capo i modelli per ogni regione; in ogni modo è necessario lavorare in rete, come accade anche nella pratica medica. Il problema sarà poi della scelta, che avviene a seconda della specifica regione, in modo da essere coerenti con le evidenze per ogni caso. I documenti preparati dalle regioni devono essere messi in comune attraverso la rete.
	PB Anche le altre regioni potrebbero di conseguenza ridurre le strutture e accreditare solo certi centri, adottando provvedimenti per ridurre le procedure.