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Design, Implementation and Usability Evaluation of a mHealth app-based Real World Data (RWD) Platform secured by Blockchain

PhD THESIS IN
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Abstract

Continuous evolution of digital health technologies is enabling and improving health data exchange and storage using tools for remote data capture and data sharing of relevant information across the health ecosystem.

In this landscape, the integration of Real World Data (RWD) into our daily lives through mobile health (mHealth) Apps becomes pivotal to reach such aims, thus increasing the value of person-generated digital health data and extracted real-world evidence (RWE).

This PhD thesis aims to: 1) Explore and understand this scenario, conducting a non-systematic scoping review to explore the pivotal role of mHealth apps in the realm of RWD collection within the context of digital health, by specifically focusing on two main aspects: the practical implementation of RWD management, and the development of such ecosystem centred around mHealth apps for RWD gathering; 2) Design and develop a mHealth-based RWD platform to provide to the end-users health & wellness services, by exploiting concepts and best practices extracted from the starting analysis; 3) Evaluate the developed solution by a usability validation of the mHealth app in a real-world use case.

The Food & Drugs Administration defined RWD in 2017 as "*data related to patient health status and/or the delivery of health care routinely collected from Electronic Health Records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices*". Mobile Health Apps (mHealth Apps) are considered a prominent source of RWD within the broader digital health landscape, thanks to their nature to run on smartphones or tablets, imbuing the RWD collection process with the property of ubiquity. They can range from targeting specific medical conditions to more general health and wellness improvement, and crucially, mHealth Apps may fall or not, based on the manufacturer's claims, under the category of "Software as medical device" (SaMD), subject to additional regulations, such as the EU's Medical Device Regulation 2017/745 (MDR).

The conceptualization of RWD involves understanding its life cycle, that encompasses several key steps, each contributing to the transformation of raw data into valuable RWE for clinical decision-making: 1) Data Creation and Collection

(Acquisition Process); 2) Data Aggregation and Enrichment (Data Management Process); 3) Data Maintenance; 4) Data Analysis; and 5) Data Usage (Real World Evidence -RWE). In this context, quality becomes an intrinsic property crucial for the effective use of RWD. Indeed, high-quality RWD can be defined as data that are intrinsically good, contextually appropriate, clearly represented, and accessible to data consumers, based on different key features: Intrinsic, Contextual (or Extrinsic), and Technical Features. Assessing quality of RWD necessitates robust tools and frameworks. For example, the Control Objectives for Information and related Technology (COBIT), and standard ISO 27001, or the Harmonized Intrinsic DQ framework (HIDQF).

Different works suggest that one of the most critical factors influencing the quality of mHealth Apps is their usability. Usability hinges on how effectively end-users, be they citizens, patients, caregivers, or healthcare professionals, can navigate and derive utility from the application.

mHealth quality can be evaluated with different tools, such as questionnaires as System Usability Scale (SUS), or Mobile App Rating Scale (MARS), or frameworks, such as the National Frameworks and Guidelines, APA Framework, or standards, such as the CEN-ISO/TS 823904-2. Moreover, ensuring mHealth apps align with established medical device guidelines and regulations, such as the MDR, is of paramount importance for cultivating such a quality perspective.

For the effective development, different frameworks and solutions were found to be useful: Patient and Public Involvement (PPI) approach, International Comparison of Evaluation Criteria (comparing mHealth app evaluation criteria from different countries), the TeleWear-AF Project Workflow, the SNApp Framework for Behavioral Health Research, the Waterfall Framework for Systematic Development, and the CeHRes Roadmap for Human-Centered Design proposed by The University of Twente.

These definitions, tools and best practices extracted from the literature review were then exploited to design and develop a RWD mobile-based ecosystem, the SynCare platform, a patient-centered mHealth-based system to collect and manage RWD, ecosystem for remote patient monitoring designed and developed executive research, with the aim to: 1) facilitate patient's self-monitoring and remote patient monitoring in chronic diseases; 2) support therapeutic alliance between patients and HPs; 3) improve patients' engagement and therapeutic adherence for chronic patients, or patients performing at-home therapies.

The main design goals were: 1) to build up secure channels for data sharing, in compliance with General Data Protection Regulation (GDPR); 2) to support the patients in the management of their own health data; 3) to clearly define the digital

health services, circumscribing the doctor-patient relationship, to guarantee the healthcare professional to report the provided services referring to specific tariffs, and defining the connected responsibilities; 4) as LifeCharger srl, to provide the above-mentioned services/ecosystem for the subscribed end-users, acting as a normal third party, without the need to view users' data without a user explicit consent.

Access to patients' data is regulated through the creation of informed, traceable, transparent, withdrawable and not tampered digital consents, that are saved as smart contracts into the Ethereum public blockchain. The patient can decide to share data with third parties, such as a healthcare professionals or an informal caregiver, by signing digital consents through the mobile app.

In the evolution of this platform from version 1.0 to 2.0, the main difference relied on the creation of the Data Analytics module.

All data stored by the LC ecosystem in these repositories is maintained in a pseudo-anonymized form, that are sent from the app to the repository for feeding the Data Analytics module, to be subsequently processed. Such module consists of a series of Python scripts triggered by various routines, executed on LifeCharger's local server to 1) Retrieve the data from the Cloud database; 2) Process the data according to the different objectives and services offered by the platform; and 3) Write back the analyzed results—still in pseudo-anonymized form—to the same Cloud database.In this way, both the clinician—via the Dashboard—and the user themselves retrieve these results for display.

The usability and acceptability validation of the designed and developed platform was implemented through a real-world use case, the e-BRAVE study, where the end-users were intended to use autonomously the mobile app based upon the developed SynCare ecosystem, in their real-world environments, thus, obtaining a usability evaluation and validation in a real-world scenario.

The e-BRAVE study was approved by the Istituto Nazionale Tumori (INT) ethics committee Act N° 30/24, and the recruitment, through the mobile BRCApp registration, started on June 28th, 2024, and it is currently undergoing, letting the volunteers download the app from Apple and Google Play Stores and begin the e-Brave study in every moment.

The BRCApp is a mobile app that represents the main end-user front-end, as part of the developed innovative digital ecosystem designed to gather cohort information, enhancing synergy between project participants and researchers. The BRCApp platform aims to support women's engagement, adherence to treatment, intervention plans, and self-empowerment, complemented by activity tracking and monitoring. Thus, the BRCApp through its Ecosystem becomes able to create

clusters of users, applying the related journey including activities to be performed in app (physiologic and body parameters to be measured, questionnaires to be filled in and informative contents to read).

After at least 7 days of BRCApp use, the Mobile Application Rating Scale (uMARS) questionnaire was administered, digitally in-App, to the e-Brave's users, to evaluate the perceived usability. The uMARS assesses different dimensions of engagement, functionality, aesthetics, information, and subjective quality by a 5-point scale, and it has been largely used to evaluate different mHealth apps, making possible comparisons in literature between different usability studies and results.

To obtain the overall usability uMARS score, the mean of each objective subscale was derived, and their means and medians computed. This score represents the objective quality of the app, while the means and medians of the two dimensions E and F represent the user's perceived quality and the future impact of this technology on the users themselves, respectively.

To evaluate possible correlations between the obtained scores of the different uMARS sections and the effective usage of the app, to demonstrate the impact of the app usability on its effective real-world usage, the Spearman's Correlation was used.

Considering a threshold (TH) representing the minimum days of usage, users were stratified into subgroups, where a value of TH=1 means including all the users independently from continuous usage. The days of use were computed by analyzing the BRCApp Logs, from the user registration date to the date of data download for the analysis. For each subgroup the Spearman's correlation was calculated, repeating it for the different section scores: the obtained Overall uMARS score (the mean of the main four sections), for the Section A (Engagement), for the Section B (Functionality), for the Section C (Aesthetics), and for the Section D (Information). In addition, the usability evaluation was conducted also by comparing two sub-groups of users extracted from the entire sample, the control and trial groups. , with a TH equal to 7.

From the beginning of the study (28th June 2024), 1546 users registered to the BRCApp, of which 81 accounts were testers, which were not considered, and 147 accounts were found as duplicates of users, that deleted and recreated their credentials, thus resulting in a total number of 1318 unique recruited volunteers.

The usability study started on 18th February 2025, and it is currently undergoing. The data for the presented analysis were extracted on 30th December 2025.

Among all the registered e-Brave study participants, 110 users have filled-in the uMARS questionnaire, and 59 of them were randomly assigned to control group, while 36 assigned to the trial.

The BRCApp information and contents, as planned, turned out to be the main means to improve end-user's eBrave study outcomes, such as the monitoring and improvement of weight and abdominal circumference, following diets and physical exercises suggestions. Indeed, the uMARS information section obtained the highest scores, both for medians, 4(3;5), for single uMARS question mean score, with a median of 5(5;5) (Item 17: reliability of the sources), and correlations with Days of Activity, thus representing a good starting point to obtain positive final outcomes. Finally, the correlation between the app's days of use and the section's uMARS score was used to evaluate the effective influence of a real app use (not just a first interaction) on the obtained usability scores. This is important to objectively evaluate the results, without taking conclusions that are decoupled from the effective usage. Indeed, this consideration is highlighted by significant correlation for Section D (Information) > 0.7 for the trial group, showing that correlations were in general statistically significant after at least seven days of use (TH=7). This matches the idea that the perceived usability is effectively influenced by a real app usage.

This thesis addressed key challenges in understanding RWD characteristics in order to develop a mobile-based RWD platform that can collect, manage and exploit these types of data, to provide to the end-users the best health & wellness service possible while maintaining a certain data quality and security during the whole life cycle, using best practices and frameworks. RWD are crucial for obtaining RWE that can be used as insights to improve the outcome of the provided health & wellness services, through the mHealth apps in the end-user's hands.

By leveraging on different development frameworks and innovative technologies such as the blockchain, a secure mHealth-based RWD platform was developed and secured, to provide to the end-users different types of health & wellness services, enhanced and fed by their own personal self-reported data.
The architecture was designed to be scalable, flexible, and applicable in different real-world use cases. Indeed, the platform has demonstrated the ability to be used in a prospective cohort study, the e-Brave study, by collecting different types of self-reported data, such as questionnaires and physiological parameters, monitoring the end-user's behaviours and trends, during app utilization. In addition, the informed digital consents were signed directly through the mHealth app and saved as a smart contract on the Ethereum public blockchain, creating a secure and not tamperable consent ledger, recoverable in each moment, ensuring that the mHealth app could share sensitive data for that purpose.

Keywords: RWD, RWE, mHealth, Digital Health, blockchain, usability, uMARS

Acronyms and Abbreviations

AES	Advanced Encryption Standard
APT	Advanced Persistent Threat
AMED	Agency for Medical Research And Development
APA	American Psychiatric Association
AI	Artificial Intelligence
API	Application Programming Interface
ATRAcT	Authentic Transparent Relevant Accurate Track-Record)
ACHILLES	Automated Characterization of Health Information at Large-Scale Longitudinal Evidence System
BIDMC	Beth Israel Deaconess Medical Center
BC	Breast Cancer
BRCA	Breast Cancer
CCPA	California Consumer Privacy Act
CeHRes	Centre for eHealth and Wellbeing Research
CEN	Comité Européen de Normalisation
CENELEC	Comité Européen de Normalisation Électrotechnique
CP	Claudio Pighini
CSV	Comma-Separated Values
CMDs	Common Data Models

CVSS	Common Vulnerability Scoring System
COBIT	Control Objectives for Information and related Technology
C4C	Cornerstones4Care
CPT	Current Procedural Terminology
DB	Database
DQ	Data Quality
DPS	Data Processing Site
DHAs	Digital Health Applications
DPROM	Digital Patient-Reported Outcome Measures
DTAC	Digital Technology Assessment Criteria
EHRs	Electronic Health Records
EVM	Ethereum Virtual Machine
EMA	European Medicines Agency
EHDS	European Health Data Space
EU	European Union
FAIR	Findable, Accessible, Interoperable, and Reusable
FDA	Food And Drugs Administration
GDPR	General Data Protection Regulation
GAD-7	Generalized Anxiety Disorder scale
GSL-TPAQ	Godin Shepard Leisure-Time Physical Activity Questionnaire
HCPs	Healthcare Practitioners
HIDQF	Harmonized Intrinsic DQ framework
HIPAA	Health Insurance Portability And Accountability Act

HTML	HyperText Markup Language
ID	Identity
IQ	Information Quality
IRB	Institutional Review Board
IDE	Integrated Development Environment
ISSP	Integrated Security, Safety, and Privacy
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
IPAQ	International Physical Activity Questionnaire
ISPOR	Internation Society for Pharmacoeconomics and Outcomes Research
INT	Istituto Nazionale Tumori
JDK	Java Development Kit
JSP	JavaServer Pages
LA	LiberActa
LC	LifeCharger
MH	Malignant Hyperthermia
MDR	Medical Device Regulation
MET	Metabolic Equivalent of Task
MARS	Mobile App Rating Scale
mHealth	Mobile Health
MFA	Multifactor Authentication
NHS	National Health System

NPS	Net Promoter Survey
O-TSK	One-Time Secret Key
PPI	Patient and Public Involvement
PPK	Patient Private Key
PGHD	Patient-Generated Health Data
PRO	Patient-Report Outcome
PROMs	Patient-Reported Outcome Measures
PA	Physical Activity
PCC	Post Covid-19 Condition
PSSUQ	Post-Study System Usability Questionnaire
QA	Quality Assurance
RCT	Randomized Controlled Trial
RE-SAMPLE	Real-time data monitoring for shared, adaptive, multi-domain, personalized prediction, and decision making for Long-Term pulmonary care Ecosystem)
RWD	Real World Data
RWE	Real World Evidence
RWP	Real World Performance
r-MEQ	Reduced Morningness-Eveningness Questionnaire
RPM	Remote Patient Monitoring
RTM	Remote Therapeutic Monitoring
RQ	Research Questions
RSA	Rivest, Shamir e Adleman
PvK	RSA private

PbK	RSA public
RBAC	Role-Based Access Control
er-MEDAS	Energy-restricted Mediterranean Diet Adherence Screener
SaMD	Software As Medical Device
SDK	Software Development Kit
SUS	System Usability Scale
SD	Standard Deviation
TAQIH	Tabular DQ Assessment and Improvement for Health
TS	Technical Specification
TH	Threshold
US	United States
UUID	Universally Unique Identifier
uMARS	user version of the Mobile Application Rating Scale
VPNs	Virtual Private Networks

Contents

Motivations and Outlines of the Thesis

The continuous evolution of digital health technologies is enabling and improving health data exchange and storage using tools for remote data capture and data sharing of relevant information across the health ecosystem, creating a continuum of care that has proven potential to enhance health outcomes by improving medical diagnosis, data-based treatment decisions, digital therapeutics, clinical trials, self-management of care and person-centred care as well as creating more evidence-based knowledge, skills and competence for professionals to support health care, reducing effectively the costs of the healthcare system [1].

In this landscape, the integration of Real World Data (RWD) into our daily lives through mobile health (mHealth) Apps becomes pivotal to reach such aims, thus increasing the value of person-generated digital health data and extracted real-world evidence (RWE) [2] [3].

Moreover, the advent of artificial intelligence (AI) is augmenting the possibility to improve the RWE obtained from RWD, to enhance clinical decision-making, clinical operations management, and population health [2].

However, many development efforts and knowledges are necessary to build this type of platforms capable to integrate RWD gathered from mHealth technologies. Risks of privacy and security become pivotal for such user-centric systems that operate on health-related sensitive data. Moreover, the quality of RWD strictly depends on the will of end-users in collecting that data: this operation must be facilitated as much as possible by improved usability of the mHealth apps.

These considerations set the need to define the requirements for a RWD ecosystem that leverages on mHealth technologies as a data collection gateway. In fact, developers are facing different challenges in building a quality system capable to handle sensitive and valuable RWD, while delivering an excellent user experience providing high quality mHealth Apps.

Consequently, the research questions (RQ) tackled in this work are the following:

1. **How Real World Data (RWD) are defined across various entities and in literature? What are the possible sources of RWD, and in this context is mHealth a privileged source to collect RWD? What are the features that define and affect RWD quality? What are the tools and frameworks used to manage and maintain RWD quality along their lifecycle?**

2. **How mHealth could improve the collection and the quality of RWD, thus improving RWE? What are the features that compose and define mHealth quality? What are the existing frameworks to assess and evaluate mHealth technology quality? What are the frameworks and best practices for mHealth real development? What are the real-world use cases and examples of RWD mHealth-based platform architectures?**
3. **How to develop a secure and innovative user centric RWD mHealth-based platform for patient monitoring? How could this platform be implemented as system that provide health & wellness service?**
4. **How can this new developed platform be evaluated by end-users in real world case scenarios? How can results of end-user's perceived usability evaluation be associated with real-world effective use? Does the perceived usability have a direct impact on real-world utilization of the mHealth developed service?**

The thesis is organized into four chapters, each addressing a specific aspect of the project. Chapter 1 introduces the background, context, and the assets to understand the other chapters, trying to answer to the first research question. This chapter will discuss the different RWD definitions found in literature, sources, quality features and the tools to assess, manage, and maintain them across the lifecycle. It will also investigate the importance of mHealth considered as RWD source to enhance RWE, considering different definitions of mHealth, its features for quality, as well as tools and frameworks to evaluate and assess them, in addition to the best practices for mHealth real development. At the end of this chapter, some computer architectures present in literature relevant to mHealth-based platforms to collect RWD will be presented.

From Chapter 2 onward, the practical and operative part of this project will be presented, and the remaining RQ will be answered. In particular, Chapter 2 will present the practical development steps of an innovative user centric RWD mHealth-based platform secured by blockchain, from the design to the implementation, highlighting the different versions (from 1.0 to 2.0) developed through this PhD thesis project. These versions represent the shift from an initial remote patient monitoring platform towards a more generalized system capable to provide health & wellness services, extending the offer from patient monitoring to psychological consultations or blood test booking (and other services…).

Chapter 3 will present the results and the analysis of the usability evaluation of the developed platform by the end-users, linking these results to the real impact on the effective real-world use of the mHealth app, and thus of the RWD collection platform.

Finally, Chapter 4 will provide the conclusion, summarizing the key findings and main contributions of this work. It also will address its potential limitations and will offer

recommendations for future research to further enhance the developed tools and approaches in mHealth development.

1 Introduction

In order to answer the initial research questions — RQ1 and RQ2 previously defined— a deep literature research, translated in a non-systematic review, was conducted, aiming to understand the concepts, tools, and real-world use cases that lay under the development of a mHealth-based RWD platform.

In this introductory chapter, Section 1.1 will provide an overview of RWD as pivotal instrument to investigate people health, highlighting its critical role to enhance real-world evidence (RWE). Section 1.2 will explain the materials and methods used to conduct the literature review, thus providing a roadmap that will drive the reader along this chapter. Section 1.3 will focus on the concepts that constitute the basis for RWD mHealth-based ecosystem development, investigating definitions, processes, and frameworks implemented for the development of such systems, with a particular focus on which features have an impact on the quality of the final product. Section 1.4 will introduce some examples of platforms developed and tested in real-world scenarios, while Section 1.5 will provide final considerations that stress the importance of comprehensively understanding and implementing processes and features to guarantee the high-quality development of RWD mobile-based platforms. Finally, Section 1.6 will draw the conclusions to link this chapter to the next, that will treat the real mHealth-based RWD system implementation.

1.1. The Real-Word Data (RWD)

Traditionally, RWD have been pivotal for assessing drug safety, therapeutic outcomes, and informing coverage and payment decisions [2] [3]. Over the last decade, there has been a significant expansion in the use cases of RWD, extending beyond pharmaceutical and real-world evidence (RWE) companies to include payors, providers, health systems, and academic institutes. The increasing utilization of RWD for artificial intelligence (AI)-assisted clinical decision-making, clinical operations management, and population health is now a best practice in the RWD life cycle [2].

A transformative force in this landscape would be the integration of RWD into our daily lives through mobile health (mHealth) Apps. These apps have not only increased the amount and significance of person-generated digital health data but have also demonstrated their potential in enhancing evidence generation. Operating on smartphones, mHealth Apps may complement traditional electronic health record data [4]. This symbiotic relationship allows for the collection of diverse RWD types

throughout the day, utilizing various smartphone-integrated sources, including other apps, connected medical devices, and embedded sensors (e.g. photoplethysmography by camera sensors [5], seismocardiography by inertial sensors [6] [7]).

Multiple regulations and guidelines by several institutions [4] underscore the intrinsic overlap between the availability of digital health technologies and the potential for RWE generation. Digital health not only provides RWE but also addresses gaps and requirements in RWE, such as necessitating data generation through innovative means, such as mobile apps [4].

Furthermore, the use of mHealth apps presents a dual advantage: 1) enriching RWE and empowering users to actively manage their health through proactive engagement, as RWD generation through these apps could contribute to the improvement in diagnosis, prevention, and treatment; 2) benefitting patients in supporting both the short and long-term self-management. From a clinician's perspective, RWD generated by mHealth app could offer a more comprehensive view of a patient's condition within visits, enabling timely interventions and reducing clinic appointments and emergency hospitalization. In addition, in the realm of research, RWD from mHealth apps can provide representative and realistic evidence in less time and monetary costs compared to a Randomized Controlled Trial (RCT).

These considerations set the stage for a better understanding of the requirements for RWD ecosystems in practical scenarios that could leverage mHealth technology as a data collection gateway. Developers are facing the challenge of navigating this context with the aim to build a quality system capable to handle sensitive and valuable data while delivering an excellent user experience, using high quality mHealth Apps.

A non-systematic scoping review [8] involves a knowledgeable selection of high-quality articles to explore a topic or answer a specific question, with the advantages of flexibility, speed, and simplicity for quickly identifying trends, clarifying a topic's scope, and providing context in areas where formal systematic reviews may not be feasible or necessary. In addition, a scoping review can be considered more suitable compared to systematic review to capture fast, dynamic and in continuous transformation fields such as that involving the scope of this research in the context of RWD [8].

Accordingly, we conducted such non-systematic scoping review to explore the pivotal role of mHealth apps in the realm of RWD collection within the context of digital health, by specifically focusing on two main aspects: the practical implementation of RWD management, and the development of such ecosystem centred around mHealth apps for RWD gathering.

This review highlighted the challenges, opportunities, and best practices associated with the integration of these technologies into the landscape of health and wellness. Through a detailed analysis of frameworks, tools, and case studies, we aimed at providing a comprehensive overview that could guide developers, healthcare

professionals, and stakeholders involved in the implementation and evaluation of such solutions, The ultimate goal was to promote a better understanding and increased adoption of effective approaches for managing and accessing the quality of RWD data collected through mHealth apps, thereby contributing to the development of reliable and user-centric digital health ecosystems.

1.2. Materials, Methods, and Roadmap for non-systematic literature review

The non-systematic literature search was conducted leveraging on Pubmed, Google scholar, and JMIR databases, using Boolean operators to refine our queries. The initial search was structured into three queries, each focusing on specific keywords: 1) "real world data", "RWD", "mobile health app", and "development"; 2) "patient reported outcome", "self-reported data", "mobile health app", and "development"; 3) "patient generated health data" and "mHealth". The results of these three searches were combined to cover as much papers as possible in this area.

To ensure a focus on the most current insights, our search was limited to studies published within the past 5 years, starting from 2018 onward, until the date the queries were first executed, on July 2023. This timeframe was chosen recognizing the rapid evolution of mHealth apps and RWD systems through technological advancements, potentially influencing data quality challenges. A second round of the same queries was executed in January 2025, to eventually add relevant missed articles and update the research to 2024.

The search was restricted to articles written exclusively in the English language, to ensure consistency and uniform understanding of the different texts. In addition to this database search, articles were sourced from the authors' archives, and relevant citations within the identified literature were also explored. Complementary to traditional searches, specific webpages were consulted, such as https://www.utwente.nl/en/bms/ehealth/cehres-roadmap-toolkit/cehres-phases/, with proposed novel frameworks that are expected to become a reference in the context of App quality assessment, such as [9], for valuable examples and to guide our literature and document search.

The approval of the articles to be included followed a meticulous process encompassing three key dimensions: originality, relevance, and quality. One reviewer (CP) initially scrutinized titles and abstracts, applying the inclusion criteria mentioned above to filter articles.

The final list was generated based on the criteria of originality and relevance to the broad scope of this non-systematic review. Our article selection process adhered to a predefined schema representing the followed conceptual roadmap (Figure 1), with the goal of emphasizing the originality of the content and its relevance to the overarching

theme of developing mHealth applications for RWD integration into patients' daily lives. Quality appraisal formed the final layer of this assessment, considering aspects such as research methodology, presentation clarity, and the presence of robust empirical evidence. The inclusion of two articles from 2016 ([10] and [11]) was deemed relevant to the overall context due to a lack of recent mHealth development frameworks in the literature.

As result of the non-systematic literature search at the first round on July 2023, the three queries in the three different databases, Google Scholar, PubMed, and JMIR, resulted in a total of 37930, 18778, and 49116 articles, respectively. At the second round on January 2025, the three same queries resulted in 39740, 18588, and 49126 articles, respectively.

After the article selection process, 37 works were selected to be relevant for this scoping review, focusing on the analysis and evaluation of quality RWD and digital m-health apps, on tools and frameworks for the implementation and development of a quality RWD mobile-based platform, and finally on interesting real-word use cases of implementation. At the end, 33 papers were identified to be coherent with our main goal, while 4 articles were discarded due to their narrow focus on designing RWE-based trials for pharmacological or epidemiological research.

Following the non-systematic literature search and the article selection process, the results were organized into three sections outlined in the conceptual roadmap depicted in Figure 1, based on the article content: 1) Understanding the Context: defining the key terms and concepts necessary to comprehend the context; 2) Concepts and Tools: exploring various concepts and providing examples of tools and frameworks that facilitate the effective development of an mHealth-based ecosystem for RWD; 3) Real-World Scenarios: examining real-world scenarios that propose architectures designed to leverage RWD.

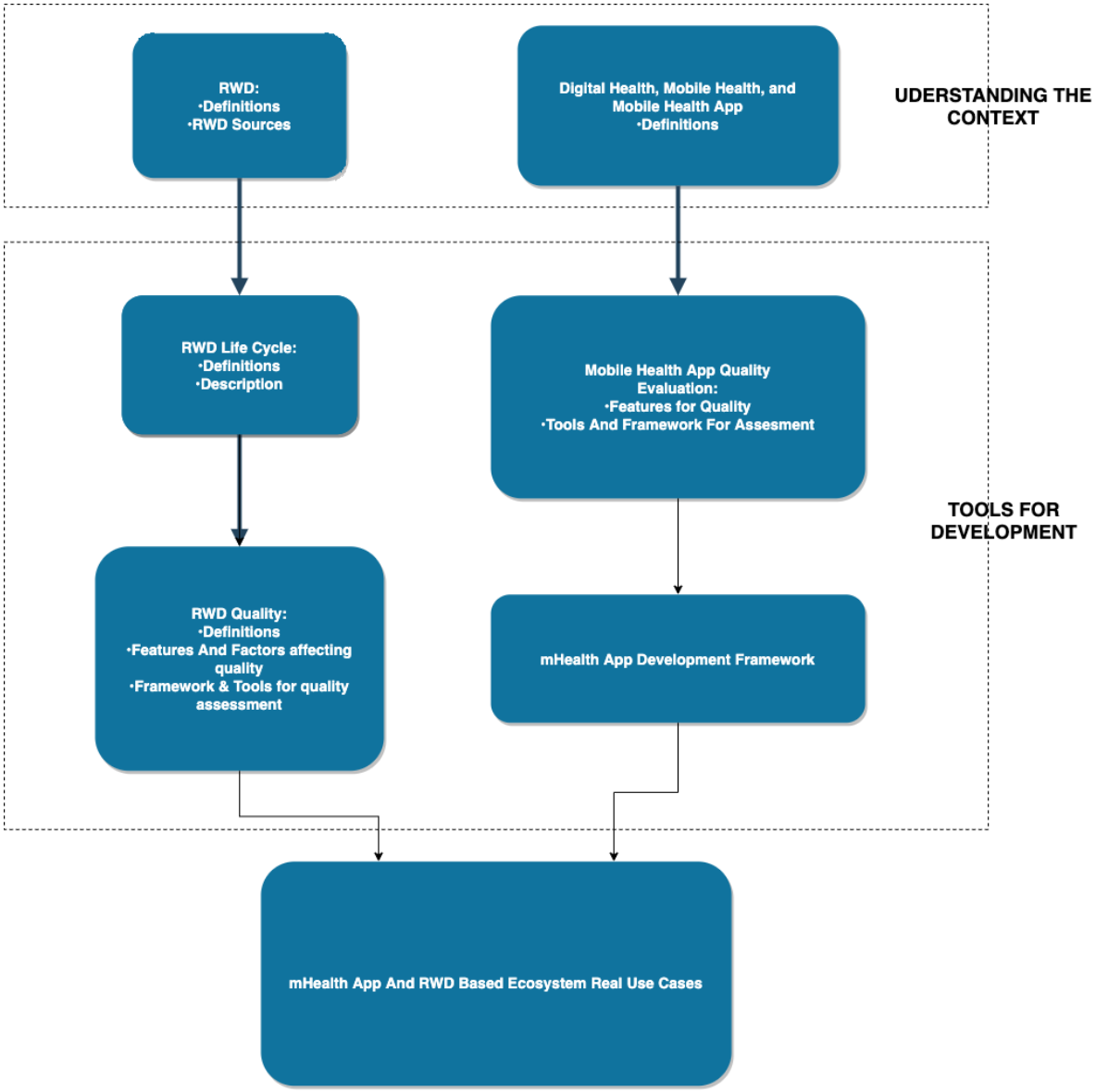

Figure 1: conceptual roadmap followed in searching for literature and categorizing relevant results

1.3. Concepts for RWD mHealth-Based Ecosystem Development

1.3.1. RWD and Mobile Health: Understanding the Context

The RWD definitions were found to vary based on their context of use. Different interpretations of RWD were found, ranging from observational data generated during routine healthcare provision, to patient-generated health data (PGHD) collected through mobile apps and wearables.

To provide a comprehensive overview, Table A 1 summarizes these definitions along with the types of RWD sources identified by various authors. Among RWD

definitions, [3], [12], [4], [13], and [14] did not cite any source. (e.g. Food and Drugs Administration (FDA)).

Patient empowerment and multiple fields of application underscore the need for a tailored RWD definition, essential for its application in the context of digital health apps. According to [2], [3], [15], and [9], RWD can be viewed as observational user health-related data reflecting actual healthcare encounters, both collected passively and actively. Importantly, this definition aligns with the passive or active collection of health data via digital tools, devices, wearables, or apps.

The Food and Drugs Administration (FDA) definition is the most frequently cited by different works [3] [16] [17] [18], and [19] (see Table A 1), and it also underlines the use of digital health technologies, such as mobile health apps, to gather health-related data. The FDA defines RWD in 2017 as "data related to patient health status and/or the delivery of health care routinely collected from Electronic Health Records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices".

These concepts of RWD collection and data aggregation from different sources are steps taking part of the RWD life cycle described in the next section paragraph 1.3.2.

Digital health is defined as tools and services utilizing information and communication technologies; it aims facilitating healthcare purposes, including diagnosis, monitoring, treatment, and prevention. Mobile Health Apps (mHealth Apps) is a prominent source of RWD within the broader digital health landscape. As per [3], [20], [21], [17], and [14], a mHealth App is defined as a software application designed for health management. It can range from targeting specific medical conditions to more general health and wellness improvement. Crucially, mHealth Apps may fall or not, based on the manufacturer's claims, under the category of "Software as medical device" (SaMD), subject to additional regulations, such as the EU's medical device regulation (MDR) [22]. This regulatory distinction acknowledges the potential impact of mHealth Apps on potentially critical health decisions. Importantly, mHealth Apps emerge as a common source of RWD, capturing data ubiquitously and integrating it with other sources, such as Electronic Health Records (EHRs), wearables, sensors, and additional apps ([17], [13]).

Moreover, the nature of mHealth Apps, designed to run on smartphones, imbues the RWD collection process with the property of ubiquity. These apps, equipped with advanced technologies, could facilitate continuous data collection throughout the day, capturing real-time insights into users' health and behaviour. The ubiquity extends beyond the clinical setting, enabling a holistic understanding of individuals' health states in their natural environments. This continuous and context-rich data collection potentially enhances the granularity and depth of RWD.

Indeed, the advances in technology surrounding mHealth Apps enable seamless integration with various data sources, fostering synergies that enrich the overall dataset. Integration with EHRs, wearables, sensors, and other health-related apps could potentially create a comprehensive user health profile. This integrated approach can provide a holistic view of individuals' health experiences and outcomes, adding some details of patient's health history that routine healthcare databases with therapy and clinical diagnoses inevitably miss [3] [23].

1.3.2. RWD and mHealth App: Concepts and Tools for Development

1.3.2.1. RWD: the life cycle, quality features, and frameworks for quality assessment

The conceptualization of RWD involves understanding its life cycle, delineating its journey from source to utilization as RWE. The process of collecting and utilizing RWD follows a structured life cycle, crucial for ensuring the quality and reliability of the data used in digital health applications. As described in Table A 2, a RWD flow can be defined starting from data collection from different sources and ending with the use of the derived information as RWE for clinical decision-making.

The resulting life cycle, as a further elaboration starting from what described in [2] and merging the different definitions as reported in Table A 2, encompasses several key steps, each contributing to the transformation of raw data into valuable RWE for clinical decision-making:

I. Data Creation and Collection (Acquisition Process):

- Description: Users actively engage with mHealth Apps, contributing data that serves as a primary source of information.
- Characteristics: Data undergo storage and transfer processes.
- Best Practices:
    - Ensure compatibility with internationally recognized data standards for effective data aggregation.
    - Implement Quality Assurance (QA) measures tailored to the specific context.
    - Incentivize detailed data entry at the source to maximize value.
    - Deploy natural language processing for mobilizing unstructured data.
    - Prioritize diversity in RWD to reduce bias and maintain equity.

II. Data Aggregation and Enrichment (Data Management Process):

- Description: Data from diverse sources are aggregated at the mHealth App level and further combined across different patients. Processing and annotation with metadata enhance data richness.

- Characteristics: Aggregation involves processing and annotation.
- Best Practices:
    - Maintain compatibility with internationally recognized data standards for effective aggregation ([2] Table A 2),
    - Integrate QA measures into the aggregation process.
    - Utilize natural language processing for handling unstructured data.

III. Data Maintenance:

- Description: Data curators oversee partitioning, data security, privacy, QA, and define data access roles.
- Characteristics: Ensuring data security, privacy, and maintaining data integrity.
- Best Practices:
    - Ensure partitioning of data for efficient management.
    - Address data security concerns to safeguard sensitive information.
    - Implement privacy measures to comply with ethical and legal standards.
    - Integrate QA processes into the maintenance phase to identify and rectify data anomalies.
    - Define clear data access roles to manage permissions and enhance data governance.

IV. Data Analysis:

- Description: Data curators design and execute the study, analysing the aggregated data.
- Characteristics: Study design and comprehensive data analysis.
- Best Practices: Implement platform solutions that enable rapid-cycle and flexible analytics ([2], Table A 2).

V. Data Usage (Real-World Evidence - RWE):

- Description: RWE derived from the analysed data is utilized by decision and policy makers for final stakeholder use.
- Characteristics: RWE application for decision-making.
- Best Practices: Protect and return value to patients through transparency, engagement, and a focus on data privacy ([2], Table A 2).

Figure 2: RWD Life Cycle Schema

The proposed data life cycle (Figure 2) description is consistent with those reported in Table A 2 and provides a good generalization of these definitions.

In the context of managing data within its life cycle, quality becomes an intrinsic property crucial for the effective use of RWD. Table A 3 delves into the multifaceted concept of data quality, outlining its features and the diverse factors influencing this critical property. Indeed, understanding these dimensions is of paramount importance for ensuring the reliability and relevance of RWD throughout its life cycle [2].

High-quality RWD is defined as data that are "intrinsically good, contextually appropriate, clearly represented, and accessible to data consumers" [24]. Let's focus into key features characterizing top-notch RWD and how they manifest across different phases of the life cycle:

Intrinsic Features (Data Acquisition):

- Completeness: this refers to the extent to which missing data about the user are present. It's crucial to ensure a comprehensive dataset that captures all relevant information. This property can be affected by patient's adherence and willingness to use the application for data entry.
- Correctness or Accuracy or Reliability: the reliability of RWD hinges on how accurately the data values reflect reality. It underscores the importance of data precision and truthfulness. These properties can be influenced by variable quality of apps and devices in their accuracy and patient's input errors, such as manual data entries that can be prone to inaccuracies or inconsistencies.
- Heterogeneity: assessing the variability in the same type of data among different users, depending on the source of data acquisition (e.g., activity data

from various wearables). Understanding and managing this diversity are key to maintaining high-quality RWD.

- Timeliness: data can be requested to the users and updated when is needed.
- Relevancy: data sample of interest is presentiveness of demographic characteristics.

Contextual or Extrinsic Features (Data Management):

- Confidentiality: data security is a critical concern, emphasizing secure storage to protect sensitive information from unauthorized access.
- Integrity: ensuring data integrity involves preventing accidental modifications that could compromise the reliability and trustworthiness of the information.
- Availability/Timeliness: timely access to data for analysis is essential for maintaining the relevance and usefulness of RWD.
- Authenticity: provenance documentation, ability to verify source, changes in data collection over time, de-identification and privacy protection.

Technical Features:

- Traceability: throughout the life cycle, traceability is crucial for providing feedback to data stewards and custodians. It facilitates the identification and rectification of any issues that may arise, contributing to ongoing improvements in data quality.
- Interoperability: leveraging interoperability standards ensures that RWD collected in various healthcare settings can be seamlessly shared, curated, and represented. This interoperability enhances the utility of RWD across different domains and disciplines, contributing to integrated and comprehensive healthcare ([24], Table A 3).

These different RWD properties to ensure quality were extracted by merging the different features and factors exposed on Table A 3, starting from the dimensions proposed by [24], and enriching the notions with other concepts from the other cited articles in Table A 3.

However, assessing the quality property of RWD necessitates robust tools and frameworks. In this perspective, three notable works were selected from the reviewed articles ([12], [24], and [19]), providing an operative process to ensure RWD quality during the data life cycle and introducing different available open-source tools and frameworks.

The framework proposed by [12] focuses on preserving data quality within the life cycle based on the Control Objectives for Information and related Technology (COBIT) framework [25, 26] and ISO 27001 standard [27]. This model aims to secure RWD by ensuring confidentiality, integrity, and timely availability for analysis. Grounded in

established standards, it articulates key elements, including meticulous access and change management, business continuity strategies, and rigorous controls for data operations. This framework addresses the second key feature identified as "Data Management" and provides operational processes based on five key elements:

- Access and Change Management: identifying roles and responsibilities for data curators, maintaining up-to-date lists of active users, and implementing Agile processes for version control. This involves roles identification, access rights provision based on roles, and Agile version control. The entire process is tracked and detailed in Table A 4
- Business Continuity Management: adoption of strategies at each step of the data journey to reduce risks and ensure workflow continuity. This includes methods of risk reduction, such as data backup, controls during data transfer, and data input operations.
- Data Operations Regarding Data Input: this includes conducting an annual external audit based on ISO 9001, implementing automatic data quality assessments, and addressing missing data through notifications on the web dashboard for healthcare professionals.
- Transfer of Patient Data: regulated transfer of anonymized patient data with documented controls for completeness and accuracy. This involves a regulated transfer of anonymized patient data from data backup to the Data Processing Site (DPS), ensuring completeness and accuracy.
- Controls for Completeness and Accuracy: implementation of methods to reduce risks during Data Acquisition and Management in RWD life cycle phases. This includes measures at different levels, from patient support to IT support, and quality control processes. The implemented measures are detailed in Table A 4.

Systematically applying this framework to the mapped processes, it allows evaluating whether the controls adhere to best described practices (i.e., COBIT and ISO 27001). Emphasizing the importance of continuous improvement, the authors in [11] recommended creating a strategy board including medical doctors, data scientists, mathematicians, statisticians, and project management leaders. Regular meetings every three months are suggested for reviewing results and implementing potential improvements.

On a parallel track, the second work [24] surveys the landscape of tools and frameworks, highlighting essential resources for intrinsic Data Quality (DQ) assessment. This review principally introduces the Harmonized Intrinsic DQ framework (HIDQF), aiming at identifying DQ properties and terminology. The authors included open-source tools that mainly address intrinsic DQ indicators as well, based on a qualitative examination of the logic and innovativeness of the

approach and whether they have been field-tested. Their results in a concise format are the following:

- Harmonized Intrinsic DQ Framework: since 2016, this framework has been offering different indicators and names to harmonize terminology and concepts so that different frameworks and studies can be compared more consistently (Figure 3 from [24]). However, it does not explicitly address contextual and process categories vital for DQ assessment and management in RWD production and curation life cycles.

Harmonised Intrinsic DQ Framework (HIDQF) categories & subcategories mapped to frameworks used by Australian agencies and other DQ studies							
HIDQF category	**Conformance**			**Completeness**	**Plausibility**		
HIDQF subcategory	***Value***	***Relational***	***Computational***		***Uniqueness***	***Atemporal***	***Temporal***
Mapping 1: DQ subcategories used by Australian agencies (AIHW, ABS & HIQA)							
DQ subcategories currently used by Aust agencies	• ***Interpretability,*** • ***comparability***	• ***Relevance,*** • ***Interpretability***	• ***Accuracy***	**Completeness**	• ***Interpretability***	• ***Coherence***	• ***Timeliness,*** • ***punctuality (compare with currency)***
Mapping 2: DQ categories & subcategories used in other DQ studies reviewed (See Supplemental file 3)							
Other DQ category	**Comparability, Linkability, Correctness**			**Completeness**	**Believability, Credibility, TImeliness, Currency**		
Other DQ subcategory	• *Representation Integrity* • *Consistency: coding, representation, internal & external, domain* • *Information loss & degradation* • *Correctness (Accuracy Elements)* • *Concordance*			• *Documentatn* • *Density* • *Representatn* • *Metadata for data element completeness*	• *Ascertainmnt* • *Duplication* • *Domain*	• *Reliability* • *Correctness* • *Consistency*	• *Currency* • *Representatn-* • *Correctness* • *Consistency*

Figure 3: "Existing harmonized intrinsic data quality (DQ) framework (HIDQF) categories and subcategories mapped to frameworks used by Australia agencies and other DQ studies. ABS: Australian Bureau of Statistics; AIHW: Australian Institute of Health and Welfare; HIQA: Irish Health Information Quality Authority" from [24]

- Quality Knowledge Repository: developed as a service-oriented architecture to store DQ concepts and methods, providing a scalable and reproducible framework for DQ assessment of different data sources.
- Web-Based Tools such as TAQIH: conducts data analysis to improve intrinsic data properties.
- Automated Characterization of Health Information at Large-Scale Longitudinal Evidence System (ACHILLES): performs DQ checks on databases aligned with the Observation Medical Outcomes Partnership Common Data Model (CMD), enabling rapid comparison of the DQ of multiple international datasets.

Additionally, ACHILLES underscores the significance of adhering to standards for data interoperability, following the Findable, Accessible, Interoperable, and Reusable (FAIR) principles, which are the guiding principles for managing research data to improve its long-term usability by both humans and machines [28].

- OHDS Data Quality Dashboard: a tool developed to standardize DQ assessment of RWD within a Common Data Model (CDM).
- FAIR Principles/Three-Point FAIRification Framework: provides practical "how-to" guidance to stakeholders seeking to implement FAIR principles.

Figure 4 shows a list of open-source tools cited by [24], beyond the listed tools above, mapped respectively to the concepts introduced by HIDQF.

Data Quality Assessment Tools			
	Conformance	**Completeness**	**Plausibility**
Open-source tools	*DAQAPO-R Package*		
	DQ^{e}-C package & completeness tracking system (CTX)		
	QKR - SQL script		
	OHDSI Achilles		
	OHDSI Data Quality Dashboard (being tested)		
	Data Curator		
	Data Cleaner		
	Talend Open Studio		
	SQL Power architect - Data profiling		
	SQL Power DQguru - Data cleansing		
	DQ analyzer - freeware		
	Pentaho Kettle		
	TAQIH (tabular DQ assessment and improvement for health)		
	EMRAdapter		
Commercial tools	*QUADRIS Qbox*		
	CESR DQA reporting system		
			MonAT visual tool
	Diameter Health Software		
	Talend Commercial		

Figure 4: "Data quality assessment tools" from [24]

Finally, [19] proposed the ATRAcT (Authentic Transparent Relevant Accurate Track-Record) framework, deeply described in [29], as set of screening criteria to assess whether potential RWD sources for planned research studies are fit-for-purpose and

of sufficient quality to support the creation of trustworthy, based on the following dimensions: authenticity, transparency, relevance, accuracy, and track-record (Figure 5). They defined these dimensions as follows: 1) Authenticity: a data source is considered authentic when its provenance is well-documented, and its authenticity can be verified with its component data sources as needed; 2) Transparency: a data source is considered transparent when the processes used in data acquisition, curation, editing, and linkage are described adequately; 3) Relevance: a data source is considered relevant when it contains the population of interest in adequate numbers and sufficient length of follow-up; and it contains the data elements required in order to implement an analysis plan of a real-world protocol; 4) Accuracy: a data source is operationally considered accurate when it can be documented that it depicts the concepts they are intended to represent, insofar as can be assured by DQ checks (i.e., the data is of sufficient quality to investigate specific research questions). Further, key data elements can be audited as deemed required; and 5) Track-record: a data source will be considered more trustworthy in general when it can document its track-record of use cases that resulted in the creation of credible real-world evidence.

In [29], the authors provided a table to apply ATRAcT, a sort of questionnaire, that can be used to verify that the data sources follow some properties inside the mentioned dimensions, enhancing the quality of RWD, in particular in the "Data Acquisition" phase of life cycle.

Dimensions	Concepts
Authenticity	• Provenance documentation: what, why, who, how, and when data was collected • Ability to verify provenance through data access • Changes in data collection over time • De-identification and privacy protection
Transparency	• Data Extraction, Transformation, and Loading • Handling of incorrect or missing data • Data linkage • Handling of free-text • Handling of changes in coding conventions • Data latency and refresh rate • Inclusion of synthetic data
Relevancy	• Sample size of the population of interest • Representativeness • Length of follow-up • Demographic characteristics
Accuracy	• Data quality (integrity) checks, including conformance, plausibility, completeness, uniqueness of patient records, and continuity of data collection • Ability to audit key variables
Track Record	• Historical performance of data set in creating credible, real-world evidence

Figure 5: table from [19] describing "ATRAcTR data quality criteria" in 5 dimensions

1.3.2.2. mHealth Apps: features for quality, its assessment, and development frameworks

In the realm of Real-World Data (RWD) collection, the significance of mHealth Apps cannot be overstated. As described in the previous paragraph, mHealth Apps serve as pivotal tool for gathering RWD. Consequently, delving into the assessment of mHealth App quality becomes paramount and there is the need to understand what are the features that makes this technology good enough, to define a good mHealth app.

Accordingly, Table A 5 summarizes the results of the non-systematic review focusing on the contextual meaning of mHealth App quality through its features that define it by merging and intersecting these concepts.

The different works on Table A 5 suggest that one of the most critical facets influencing the quality of mHealth Apps is their usability. Usability hinges on how effectively end-users, be they citizens, patients, caregivers, or healthcare professionals, can navigate and derive utility from the application. For instance, studies such as [30], [21] and [31] underlined the pivotal role of the usability and ease of use perceptions among end-users. We can extract from these works some factors to be considered in a usability assessment:

- Intuitive Navigation: the app's interface should be intuitive, allowing users to easily access features and information without confusion. This ensures a positive user experience and contributes to the overall usability of the app.
- Efficient Task Completion: users should be able to perform essential tasks efficiently within the app, such as inputting data, accessing health information, or communicating with healthcare professionals.
- Accessibility: a high-quality mHealth App considers diverse user needs, including accessibility features for individuals with disabilities, ensuring inclusivity in its design.
- User Feedback: incorporating mechanisms for users to provide feedback about their experience can guide continuous improvement efforts, aligning the app more closely with user expectations.

From works on Table A 5, we can also extract some features that can be used to evaluate the quality of mHealth applications from a technical standpoint. This involves several key aspects, each contributing to the overall level of quality, including:

- Privacy and Security: data security is fundamental to ensure the protection of user-sensitive information. Privacy considerations include proper management of personal information and compliance with relevant regulations.
- Interoperability: the app's ability to interoperate with other systems and data, such as electronic health records (EHR), is crucial for an integrated digital ecosystem. Also, verification of compliance with standards and specifications to ensure effective interoperability.
- Software Performance: the efficiency and performance of the software directly contribute to the user experience. This includes measurement of performance, app size, and efficient management of technological resources.
- Data Sharing Capabilities: the ability to securely share data in compliance with regulations is a key element to ensure transparency and usefulness of collected information. This includes the examination of data sharing functionalities within the app and with other healthcare systems.
- Transparent and Clear Consent for Data Usage: clarity and transparency regarding the purposes of data usage are essential to obtain informed user consent. This includes assessment of how the app communicates and obtains consent for the use of user data.

Moreover, in the realm of mHealth applications, we can consider that economic factors also play a pivotal role in shaping user perceptions and app quality, as highlighted in [14] and [30]. The following aspects, extracted from Table A 5 papers analysis, highlight the intersection of such economic factors and mHealth app quality:

- Understanding Reimbursement Impact: the availability of reimbursement options significantly influences how users perceive the quality of an mHealth app. Financial incentives, discounts, or reimbursement opportunities contribute to an enhanced perception of app quality, establishing a positive correlation between economic factors and user satisfaction.
- User Engagement and Incentives: economic incentives prove to be a powerful driver of user engagement. When mHealth apps incorporate financial benefits or rewards for consistent use, users are more likely to view the app favourably, recognizing the economic value embedded in their interactions.
- Assessing Value for Money: users often evaluate mHealth apps based on the perceived value for money. The economic advantages offered by an app, such as contributing to reduced healthcare costs or delivering tangible benefits, contribute positively to the overall assessment of value.
- Considerations of Accessibility and Affordability: the economic accessibility of mHealth apps, including factors like costs or subscription fees, significantly impacts user adoption. Apps that strike a balance between offering valuable services and being affordable tend to garner positive perceptions from users.
- Exploring Economic Sustainability: examining the economic sustainability of an mHealth app is a critical dimension of quality assessment. Clear and transparent economic models not only instil confidence in users but also reflect the reliability and long-term quality of the app.

Finally, from the analysis of Table A 5, we can state that the quality of mHealth applications, which exploit RWD, is intricately linked to the use and quality of RWD they gather. This interdependence is highlighted by the following key considerations:

- Quality Indicators Derived from RWD: the data collected by mHealth apps serve as the foundation for various quality indicators. Assessing the reliability and accuracy of RWD becomes paramount as these indicators directly influence the overall quality perception of the app. High-quality RWD contributes to robust analytics and insights, enhancing the app's efficacy.
- Pre/Post Market Surveillance: the evaluation of mHealth apps extends beyond their initial launch. Continuous assessment, particularly for post-market surveillance, relies heavily on the quality of RWD. Monitoring real-world performance and user interactions through reliable data sources becomes instrumental in identifying potential issues, ensuring user safety, and facilitating ongoing improvement.
- Defining App Purpose and Data Analysis: the purpose of an mHealth app is intricately linked to the nature and quality of the RWD it collects. Clearly defining the app's objectives, especially regarding the manipulation of patient-generated data, sets the stage for meaningful data analysis. The methods and

scopes of data analysis are directly influenced by the quality and relevance of the gathered RWD.

- Ensuring Data Quality Across the Life Cycle: adhering to best practices for RWD management, as discussed in the section 1.3.2.1, becomes a critical component of mHealth app quality. From data acquisition to storage and analysis, each phase benefits from a comprehensive approach to data quality, ultimately enhancing the app's overall performance.
- Strategic Utilization of RWD: the strategic incorporation of RWD into the development and enhancement of mHealth apps is essential. Understanding the nuances of RWD quality allows app developers to make informed decisions, tailor functionalities to user needs, and align app capabilities with real-world healthcare scenarios.

Thus, the synergy between mHealth app quality and RWD underscores the significance of robust data practices, contributing to the effectiveness, reliability, and user trust in these digital health solutions.

From mHealth quality conceptualization to its technical assessment, various methods for quality evaluation were found in literature, contingent on the specific property of mHealth Apps under consideration:

- A/B Testing for Feature Comparison: [20] introduces the concept of A/B testing as a valuable method for comparing two system features or Patient-Reported Outcome Measures (PROMs) used by the app. A/B testing offers a practical means to assess the impact of different features on user experience and outcomes, aiding developers in refining and optimizing app functionalities [32].
- System Usability Scale (SUS) Questionnaire: The SUS questionnaire evaluates the usability of mHealth apps [20]. Widely adopted in literature, the SUS questionnaire provides a standardized measure for comparing app usability across a diverse user base, facilitating robust usability assessments [33].
- Mobile App Rating Scale (MARS): [20] recommends the use of MARS for assessing the overall quality of mHealth apps, comparing them against established benchmarks. Leveraging the App Stores' ratings, MARS serves as a valuable tool for developers and users alike, offering insights into the app's performance and standing within the market [34].
- National Frameworks and Guidelines: different countries employ distinct frameworks to evaluate app quality. Examples include Germany's FAST TRACK framework and Belgium's three-level pyramid framework [21]. Compliance with national frameworks ensures that mHealth apps meet regulatory standards, enhancing their perceived quality and fostering user trust.

- APA App Evaluation Framework: the APA framework specifically evaluates psychological and psychiatric mHealth apps across five levels [14]. Tailored for mental health apps, this framework provides a structured approach to assessing and selecting apps based on psychological considerations.
- Net Promoter Survey (NPS): the NPS gauges user satisfaction on a scale of 1-10, providing valuable insights into user sentiments [35]. NPS offers a straightforward metric for evaluating user satisfaction, aiding developers in understanding and addressing user concerns.
- CEN-ISO/TS 823904-2: [9] presents a framework of 81 questions for assessing mHealth App quality. 67 (83%) of which impact the scores of 4 quality aspects: "Healthy and Safe", "Easy to use", "Secure Data", and "Robust Build" (Appendix 8). Manufacturers estimated 2-4 days to complete the assessment and gather evidence.
- mHealth Engagement framework evaluation: [36] investigated chronic users affected by diabetes using RWD collected by mHealth App. Their proposed a 4-steps user journey along the use of the App and quantified user engagement by different metrics based on that journey.

In essence, the quality of mHealth apps is a multifaceted construct, intricately tied to real-world usage, technical robustness, economic considerations, integration with RWD, and adherence to regulatory standards. The discussed tools and frameworks serve as invaluable resources for developers, healthcare professionals, and end-users seeking to navigate and contribute to this evolving landscape of mobile health technology.

Table A 6 shows the list of all the tools and frameworks cited above.

In addition, ensuring mHealth apps align with established medical device guidelines and regulations is integral to cultivating a perspective of quality. The adherence to these regulatory frameworks not only implies compliance but also encompasses several aspects that collectively enhance the overall quality of these digital health solutions:

- Certification of Quality Assurance: Conforming to medical device guidelines, such as the European Union (EU) Medical Device Regulation (MDR) 2017/745, effective since 2021 [22], provides a certification of quality assurance. This certification becomes a testament to the app's commitment to meeting predefined standards, assuring users, healthcare professionals, and regulatory bodies of its reliability.
- Patient Safety and Data Security: Guidelines and regulations often emphasize aspects related to patient safety and data security. Adhering to these standards ensures that the app incorporates robust measures to protect user data, maintaining confidentiality and integrity throughout the app's lifecycle. An

example is the General Data Protection Regulation (GDPR) for the European Union [37].

- Quality Frameworks for App Development: Regulatory frameworks may introduce quality evaluation frameworks tailored for app development. For instance, the implementation of a FAST TRACK framework in Germany, as mentioned in [21], illustrates how adherence to such frameworks contributes to the quality assessment of mHealth apps.
- National and International Alignment: Following national and international guidelines fosters alignment with broader healthcare objectives. Apps that adhere to these standards are more likely to contribute meaningfully to the larger healthcare ecosystem, ensuring seamless integration and collaboration with existing healthcare infrastructure.
- Addressing Safety Concerns: Regulatory guidelines are often designed to address safety concerns associated with healthcare applications. This includes considerations for potential risks, adverse events, and mitigation strategies, all of which contribute to the overall safety and quality profile of mHealth apps (e.g. the MDR 2017/745).
- User Trust and Confidence: Compliance with guidelines and regulations enhances user trust and confidence. Users are more likely to engage with and rely on an mHealth app that demonstrates a commitment to meeting established standards, fostering a positive user experience.

Table A 7 describes insights from various review papers, presenting a spectrum of tools and frameworks that can be crucial for the effective development of mHealth apps and mHealth app ecosystems within the digital health context. These tools, drawn from the collective findings of the reviewed literature, could serve as valuable resources for developers aiming to create robust and impactful mHealth solutions for RWD collection and management. Moreover, Table A 7 provides a detailed exploration of these frameworks, offering insights into their methodologies and applications within the dynamic landscape of mHealth app development. Here, a list that summarizes these frameworks:

- Patient and Public Involvement (PPI) Approach: [38] introduces an innovative approach emphasizing the active inclusion of end-users throughout the app development lifecycle. PPI framework advocates for incorporating user perspectives in both the design and evaluation phases, ensuring that the app aligns with the needs and preferences of its intended audience.

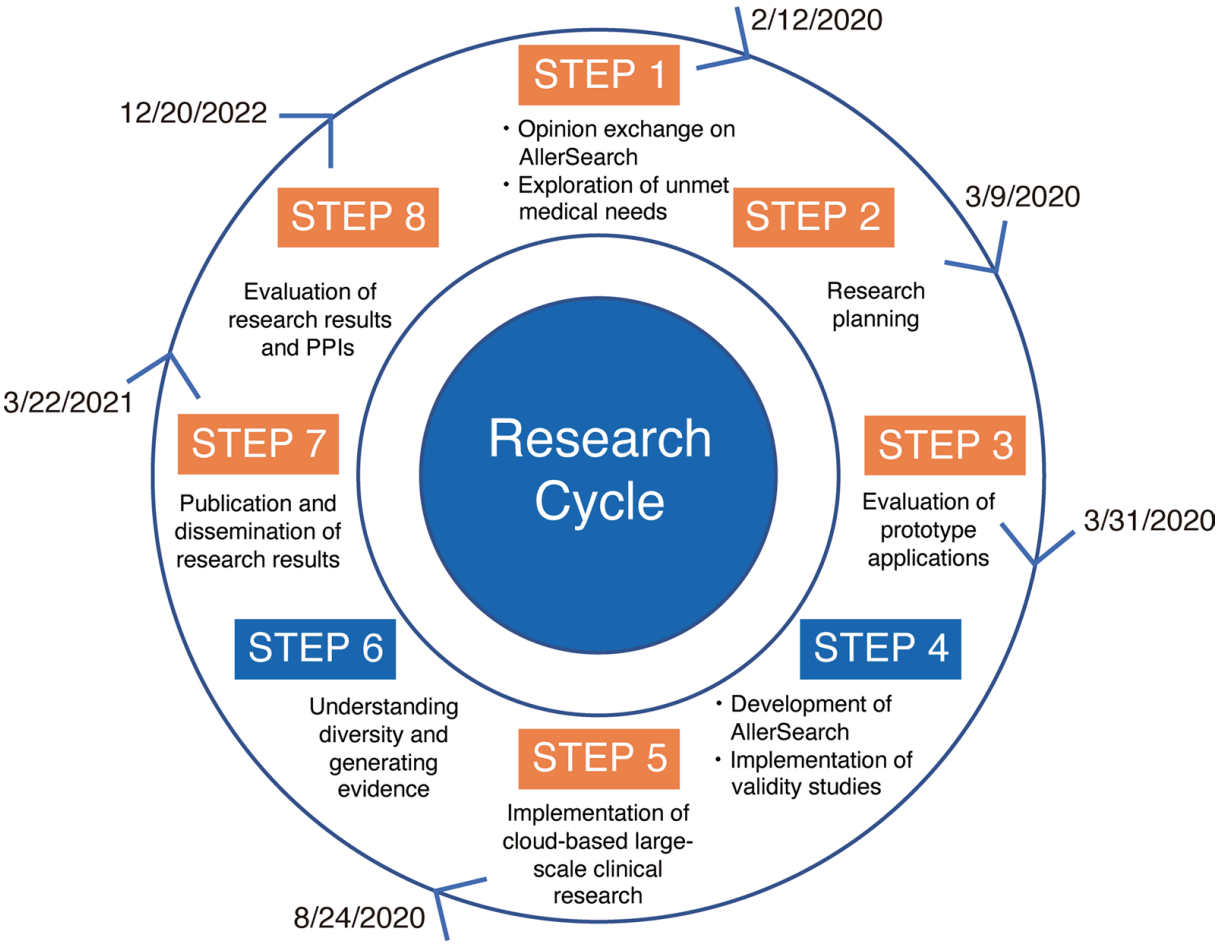

Figure 6: "Schematic of the eight steps for PPI implement in this study based on PPI Guidebook. A consistent PPI meeting was held with eight steps reference to PPI Guidebook published by the Japan Agency for Medical Research and Development. The discussion proceeded by identifying which step we are currently following based on these eight steps. STEP 1, 2, 3, 5, 7, and 8 highlighted in orange were done with the PPI committee members, and a timeline is provided for each step. PPI, patient and public involvement" from [38]

- International Comparison of Evaluation Criteria: [21] focuses on comparing mHealth app evaluation criteria from different countries. The identified criteria serve as valuable guidelines during the development phase, offering insights into internationally recognized standards and expectations for app quality (see Table A 7 for in-depth analysis)
- TeleWear-AF Project Workflow: [5] presents a comprehensive workflow for evaluating the development of a mHealth app, particularly demonstrated in the context of the TeleWear-AF project. The workflow encompasses usability testing, feasibility studies, randomized controlled trials (RCT), and evaluation in clinical practice, providing a structured pathway for app development.

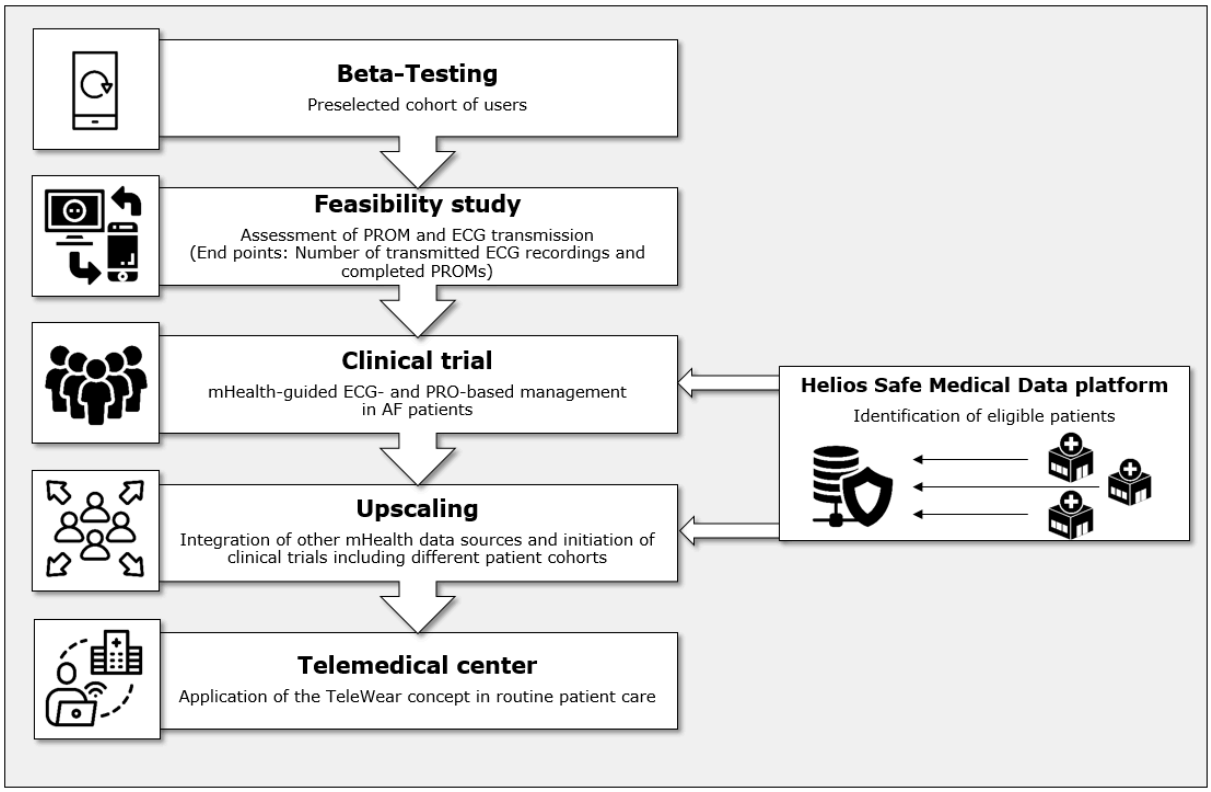

Figure 7: "Phases of the TeleWear project. Currently, the TeleWear feasibility study is conducted, followed by a multicenter randomized controlled trial including patients with AF. AF: atrial fibrillation; ECG: electrocardiogram; mHealth: mobile health; PRO: patient-reported outcome; PROM: patient-reported outcome measure" from [5]

- SNApp Framework for Behavioral Health Research: [11] offers a guide for developing and implementing mHealth apps tailored for behavioral health research. This framework highlights the importance of involving IT competencies throughout the development process, from initial design studies to implementation and maintenance.

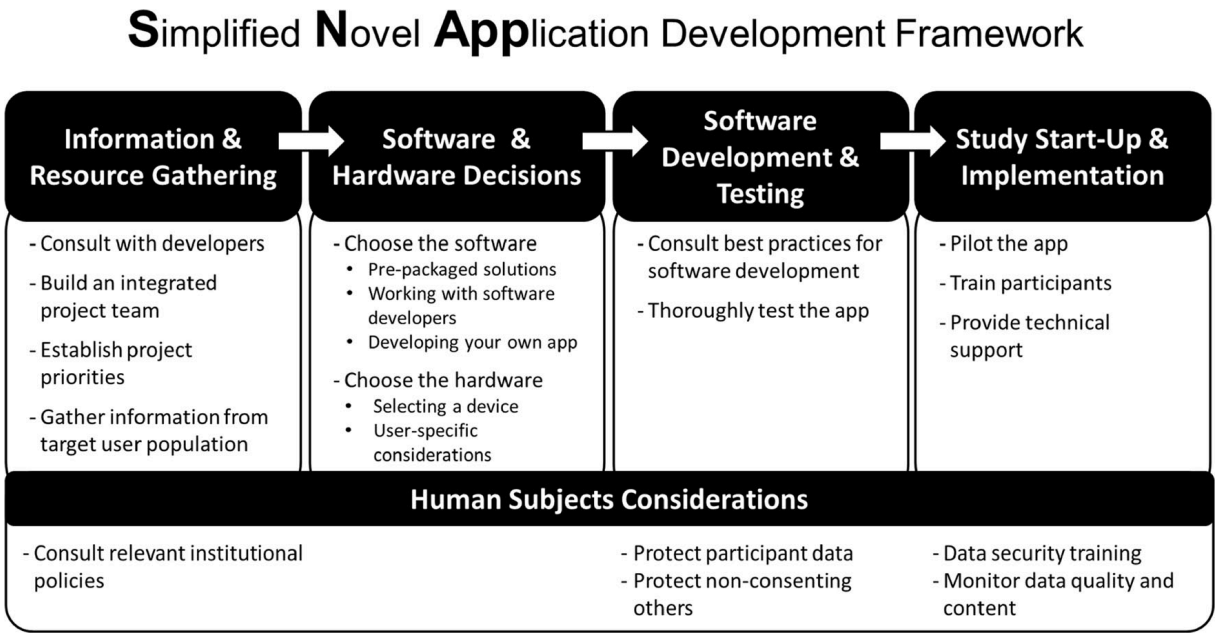

Figure 8: "The Simplified Novel Application (SNApp) development framework" from [11]

- Waterfall Framework for Systematic Development: [10] introduces the "Waterfall" framework, a systematic approach that divides the development process into seven domains. The first three domains strategically define app purposes and stakeholder goals, while the subsequent domains establish behavioral interventions. The final step translates these interventions into concrete features and app content, resulting in the finished product.

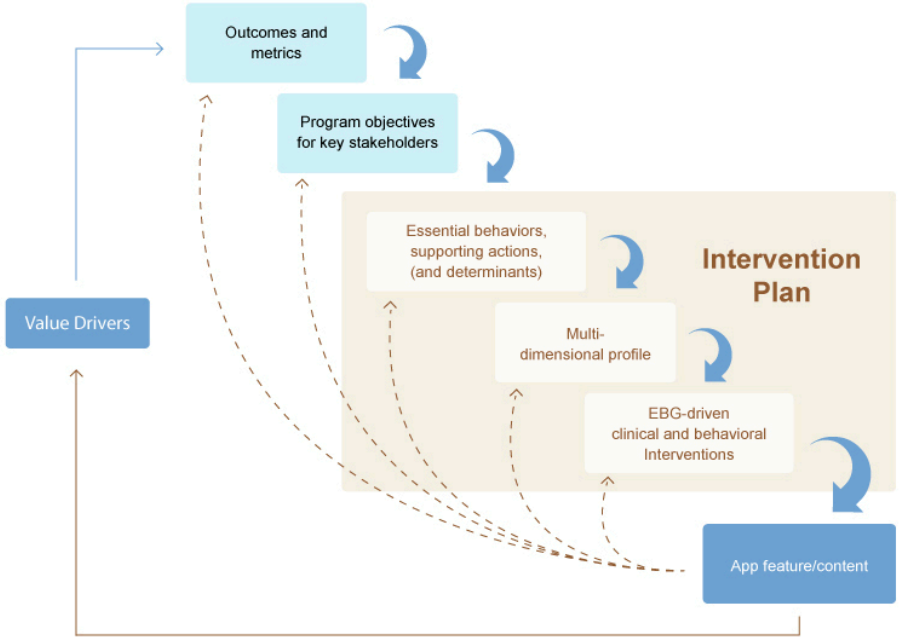

Figure 9: "mHealth waterfall process" from [10]

- CeHRes Roadmap for Human-Centered Design: The University of Twente proposes the CeHRes Roadmap (https://www.utwente.nl/en/bms/ehealth/cehres-roadmap-toolkit/cehres-phases/), an eHealth development roadmap grounded in persuasive and human-centered design principles. This framework advocates for formative evaluations conducted iteratively throughout development and at the implementation's conclusion. The formative evaluation serves a dual purpose: backward evaluation, checking outcomes of previous phases, and forward evaluation, continuously gathering stakeholder perspectives to inform ongoing processes. This iterative approach ensures ongoing monitoring and stakeholder input, representing a fundamental aspect of eHealth technology development

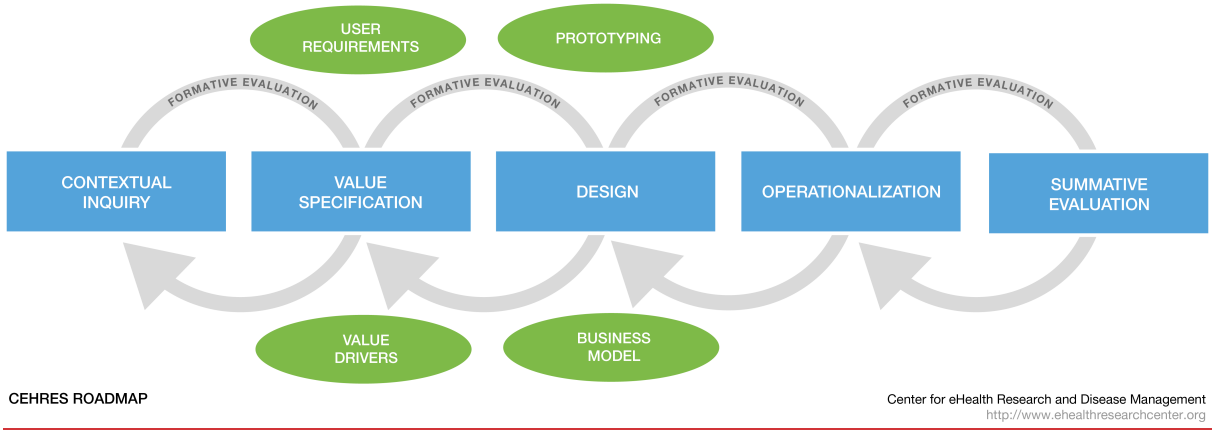

Figure 10: "CEHRES roadmap" from https://www.utwente.nl/en/bms/pht/research/cehres-roadmap-toolkit/cehres-phases/

Figure 11 provides a summary of the various phases that include the cited frameworks. These development methodologies share a common principle: involving end-users and stakeholders as extensively as possible throughout each step of the process. Additionally, they are all iterative in nature, emphasizing continuous development based on the outcomes of preceding steps.

The primary distinction among these frameworks lies in the contexts for which they are best suited. For instance, frameworks such as [38], [5] and [11] are more closely aligned with research-oriented contexts, whereas [10] and the CeHRes Roadmap (https://www.utwente.nl/en/bms/ehealth/cehres-roadmap-toolkit/cehres-phases/) are more broadly applicable to mHealth app development.

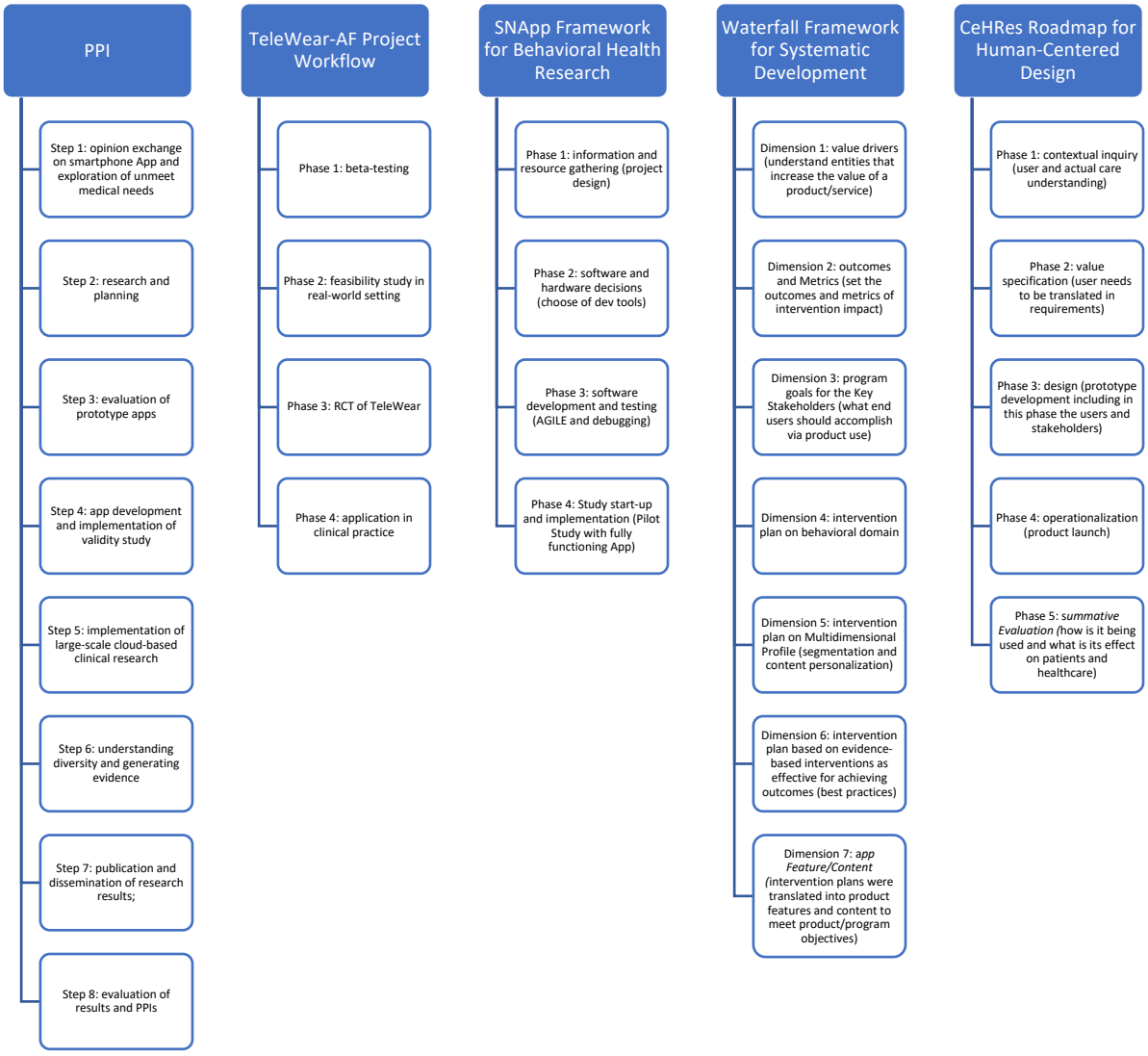

Figure 11: mHealth development framework phases

From the security and privacy perspective, the practices described by [23] offer a broad range of recommendations and tools that can be used to develop a RWD system starting from the principle of security and privacy by design. They underlined the importance of securing systems that collect and manage personal-generated health data (PGHD), suggesting interesting best practices, such as end-to-end encryption, authentication methods, and policy compliance, but also complex techniques, such as homomorphic cryptography, differential privacy, blockchain use, etc… that together can be seen as a framework to maintain integrity and confidentiality of PGHD in RWD ecosystems. These recommendations are:

- Restrict Access to Data and Applications:
    - Multifactor Authentication (MFA) (passwords, fingerprints, etc…);
    - Role-Based Access Control (RBAC) according to responsibilities;

    - Least Privilege Principle: access to level required to perform duties;
    - Routine Audits: identifications of security vulnerabilities and control of access protocols;
    - Firewall: measures against illegal network invasions;
    - Virtual Private Networks (VPNs): security of remote accesses;
    - Continuous Update and Software Maintenance.
- Implement Data Usage Controls:
    - Robust Access Controls: restrict visibility to authorized users;
    - Encryption for data integrity;
    - Audit Trails: ensure accountability;
    - Adherence & Compliance to HIPAA and GDPR
    - Policies and Procedures continuously updated: to align with legal & ethical norms;
    - Training Person about Protocols;
    - Informing Patients about their rights and the extent of their control over personal data;
    - Involvement of Stakeholders;
    - Use of Feedback Loops;
    - Individual Access to PGHD in Real-Time and Electronically: transparency and data control;
    - Clarify Informed Consent Processes about data usage sharing and possibility to modify consent in a second moment;
    - Possibility to share data for research maintaining privacy.
- Logs and Monitor Use:
    - Log Who and When PGHD are accessed;
    - Proposal of Machine Learning Techniques to identify access anomalies and data breaches.
- Encrypt Data at Rest and in Transit:
    - Encryption of Non-Data Files: proposal of two-level encryption with passcode lock
- Secure Mobile Devices:
    - Problem of Using Mobile Devices by Healthcare Providers and Patients (device theft, insecure apps, inadequate security management);

  - Recommendations about administrative measures, physical security, secure data exchange, updates, training personnel.

- Mitigate Device Connected Device Risks:
  - Devices connected to internet are vulnerable, thus, it is better to be compliant with regulations (eg. FDA).
- Conduct Regular Risk Assessments:
  - Proposal of a Framework for Risk Assessment called Integrated Security, Safety, and Privacy (ISSP) Risk Assessment Framework for medical devices with respect to device classification: systematic approach that uses calculation of ISSP score and it is based on FDA recalls and incorporates Common Vulnerability Scoring System (CVSS).
- Educate Healthcare Staff:
  - Training programs about cyber security

1.4. Real-World Scenarios and Implementations

After having explored and summarized the notions regarding using mHealth for RWD and the concepts for the development of such ecosystems, Table A 8 describes real world scenarios and implementation of RWD-based ecosystem by showing some examples of effective development in the digital health context.

For the scope of this study, two types of real-world scenarios, as outlined in Table A 8, were mainly considered: 1) the real-world implementation with a focus on managing RWD throughout its journey, and 2) an ecosystem centered around mHealth apps for the collection of RWD.

1.4.1. Real-World Implementation and RWD Management

The implementation described in [12] provides an exhaustive examination of the complete RWD data life cycle. The authors delve into the associated management and monitoring processes, spanning data acquisition to utilization in clinical decision-making, and elucidate the underlying system architecture. The paper details how to craft an effective RWD data management plan, considering risks and data quality. It introduces a strategy board and defines the data journey. Furthermore, the authors advocate for standards facilitating RWD quality certification, a key focus of this paper. Methods such as pseudo-anonymization are also proposed to safeguard data privacy.

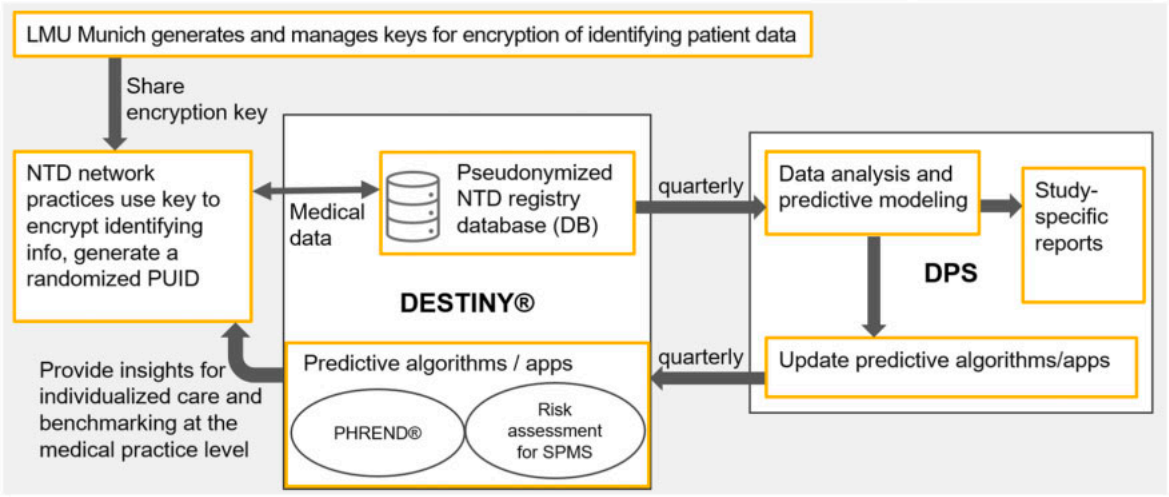

Figure 12: "Overview of the components of the registry and analytic site and the data flow in the field of multiple sclerosis (MS). Results from predictive modeling feed-back into the DatabasE-aSsisted Therapy decIsioN support sYstem (DESTINY®) every 3 months to support treatment decision making in the real world. DPS: data processing site; LMU: Ludwig Maximilians Universit€ at; NTD: NeuroTransData; PUID: patient unique identifier; SPMS: secondary progressive multiple sclerosis." from [12]

1.4.2. Ecosystem Based on mHealth App for RWD Gathering

The works of [18] and [5] described the implemented RWD ecosystem focusing on the mHealth as RWD source.

In [18], the authors illustrated a European research project called RE-SAMPLE (Real-time data monitoring for shared, adaptive, multi-domain, personalized prediction, and decision making for Long-Term pulmonary care Ecosystem) that used RWD for digital therapeutics/clinical intervention. They proposed an architecture in which Healthentia Mobile App represents the main entry point for the patients/citizens, while a Web portal is the main entry point for the healthcare professionals. The central component of this ecosystem are the cloud services, for managing and analyzing the collected RWD and provides clinical pathway services, and virtual coaching to primary end-users.

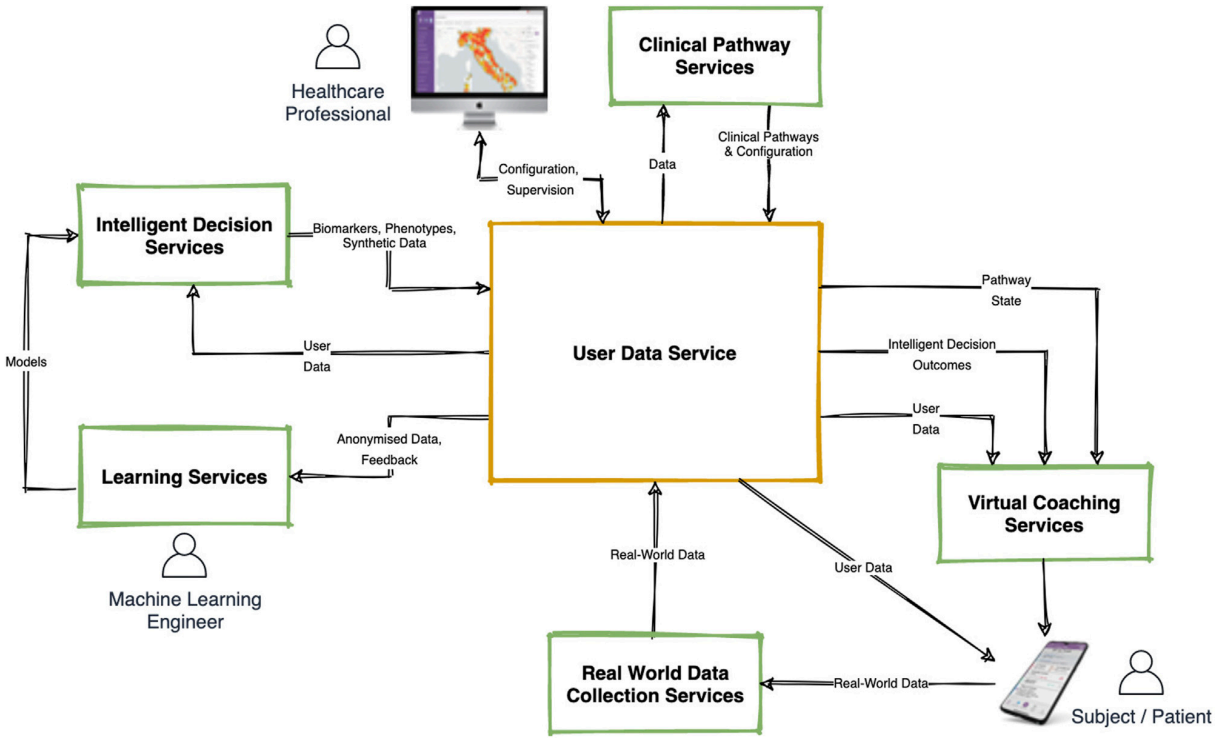

Figure 13: "High-level architecture of the proposed Digital Therapeutics platform." from [18]

In [5], the authors presented a mHealth App (TeleWear) based ecosystem for remote patient monitoring and management that aims to collect Patient-Reported Outcomes (PROs) and ECG data through integrated wearables or built-in smartphone apps. Collected data are sent to clinician frontend and reviewed by designated cardiologists. TeleWear features an application programming interface (API) for extensive customization, facilitating the integration of various data sources and the addition of questionnaires. The app allows data exchange with platforms like Apple Health and Withings Health Mate, showcasing its role in acquiring and aggregating diverse sources and types of RWD. Table A 8 treats in detail these cited works.

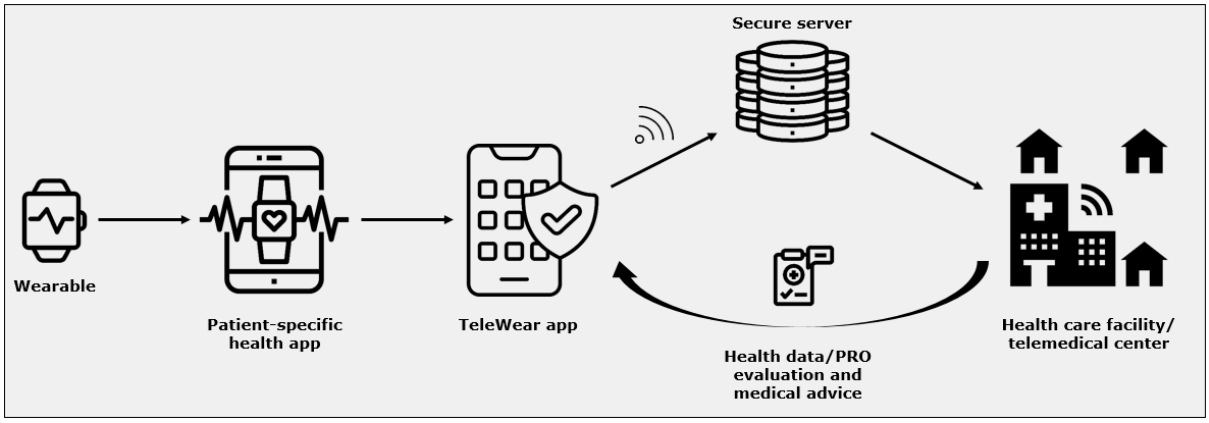

Figure 14: "Data flow. Schematic illustration of the dataflow within the TeleWear infrastructure. Patients record health data (eg, electrocardiograms) with wearables that connect to a specific health app on the patients' smartphone (eg, Apple Health). If data access is allowed, the TeleWear app collects these health data and transmits them to a health care facility or telemedical center (TMC) via a secure server connection together with patient-reported outcomes (PROs), where evaluation can take place. The patient receives medical advice by TMC physicians using the preferred communication channel (eg, telephone call, video consultation, direct messaging, or email)." from [5]

1.4.3. ELAROS DPROM Platform for Post Covid-19 Condition

Finally, in [39] the authors described a e real-word implementation of a Digital Patient-Reported Outcome Measures (DPROM) platform by adapting a pre-existent Digital Bladder Diary for remote assessment and diagnosis of lower urinary tract symptoms developed by ELAROS company. They described the process from the design to the development of a mobile app-centred platform able to administer digital PROM to patients affected by Post Covid-19 condition. Of interest is the use of PPI framework [38] to design the solution and the automatic pseudo anonymization approach to share data for research inside and outside the platform, managing the consent digitally using the clinical web portal. They also disclosure the number of users and clinics using their platform after the development with usability evaluation results, but without citing any tool or method used for this evaluation. Table A 8 describes the whole implementation, from the design to the usability evaluation of the solution.

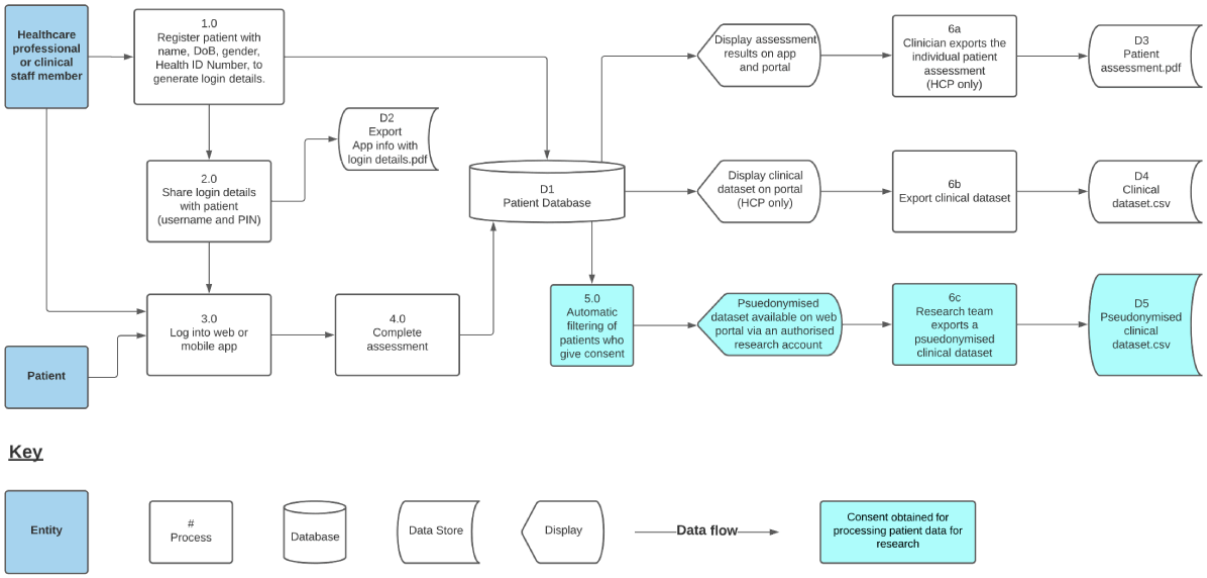

Figure 15: "Data flow in the ELAROS digital patient-reported outcome measures platform. DoB: date of birth; HCP: health care professional; PIN: personal identification number." from [39]

1.5. Considerations

In this context of dynamic and continuously evolving technologies, quality must be considered as a fundamental keyword to manage the impact of these innovations in terms of health, social, economic, and energy prospective. Quality can be defined through the definition of intrinsic and contextual or extrinsic features, that make something "intrinsically good, contextually appropriate, clearly represented and accessible to data consumers" (from paragraph 1.3.2.1). For example, RWD intrinsic features that affect quality are defined in the context of Data Acquisition process, strictly conditioned by the data nature and how data were collected, or more, extrinsic features of RWD could depend on how "externally" are managed. The same considerations can be applied to mHealth technologies. Indeed, the usability of a mHealth device, that can be considered a purpose-based designed and developed intrinsic feature, affects the end-user's perception related to the degree with whom the mHealth tool is considered "intrinsically good, contextually appropriate, clearly represented and accessible to data consumers".

Moreover, the quality concepts related to mHealth for RWD reinforce quality of RWE, helping the proliferation of digital health and data accumulation, opening new possibilities to engage patients in self-management of their chronic diseases in ways that did not exist in the past, followed by more realistic applications of digital therapeutics, supported by artificial intelligence and machine learning technologies.

With the help of mHealth-based RWD platforms, these considerations address the specific needs of different demographic groups to improve the representativeness of the RWE, reducing the racial and economic disparities. mHealth will contribute to the body of RWE from other sources and, for this reason, health app data should be reported in a standardized and comprehensible way, integrated into existing databases, proving the security and transparency towards suppliers of this personal valuable data. In this direction, the European Health Data Space (EHDS) – in particular Article 31 of the proposed regulation [40] – foresees the use of a voluntary label for wellness applications that are interoperable with electronic health record (EHR) systems. The Label2Enable project (2022–2024) has directly contributed to this provision by developing and testing an evaluation framework based on the CEN-ISO 82304-2 standard for health app quality and reliability [41]. This framework supports citizens, healthcare professionals, payers, and regulators in identifying trustworthy, legally compliant, and safe apps, and provides the methodological basis for the voluntary EHDS label.

Moreover, clinical research accelerates upon patient-reported data, that could be optimally analyzed and reach similar conclusions of randomized trials. In fact, when RCT are not feasible (expensive), registry-based real-world studies hold great promise to allow for high-quality evidence generation. Moreover, RWD implementations will raise valid concerns about e-waste and energy use, against paper and fuel and impact of virtual care and remote diagnostics reducing costs associated with in-person visits and, in general, for RCTs-based research.

These considerations are supported by the increasing interest of small start-ups as well as large tech companies such as Apple, Amazon, and Google, in the healthcare arena, underlining the value of collecting Patient (or Citizen/Person) Generated Health Data (PGHD), and contributing to advancements in analytical methods required to make sense of vast quantities of data [3].

In addition, European and US guidelines and regulations are more and more moving into the direction of exploiting RWD for medical device pre- and post-market approval, such as SaMD, for real world performance (RWP) monitoring. This implies that manufactures and developers will face the adoption of standards and guidelines that undertake processes of RWD quality control and management. Finally, RWD are also relevant to the lifting of devices from EU certification under legacy regulations to the updated regulatory approvals, in the so-called transition period for older digital health applications (DHAs), between 2021 and 2028 [20].

Thus, it is particularly important to ensure that well tested and quality methodology underpins the development of mHealth-based RWD ecosystems, with the advance of digital development that will facilitate the integration of rich and relevant personal information into traditional healthcare team focused data.

1.6. Conclusions

This review study drove us along the conceptual roadmap of Figure 1, aiming to answer to the RQ 1 and 2 previously described in "Motivations and Outlines of the Thesis" chapter. The review path started from the RWD and mHealth technologies conceptualization, that underlined the importance of DHAs as privileged sources of RWD collector. This first part aimed at finding how RWD can be defined based on literature, and in which way mHealth technologies could improve RWD collection, through their ubiquity and embedded advanced technologies (sensors, internet, etc.). Furthermore, the definition of quality for these technologies was explored, flanked by the extraction of the features that characterize it for both RWD, along its lifecycle, and DHAs, as a tool to improve the RWD collection, understanding the intrinsic influence on RWD quality induced by using mHealth as RWD collector. This analysis allowed to answer to RQ 1 about how RWD quality is defined, in particular how intrinsic and contextual or extrinsic features could affect what can be considered "intrinsically good, contextually appropriate, clearly represented and accessible to data consumers". By defining these features, it was possible to deduce what are mHealth features that consequently could affect intrinsic and extrinsic features of RWD, such as mHealth usability.

Then, the tools and frameworks that could allow the best practices in management and maintenance of a certain level of quality along the whole RWD lifecycle were explored, highlighting the most used methods and best practices in literature, and answering to the relevant part of RQ 1 and RQ 2 with a list of tools and frameworks that the developer could choose, depending on the development design (paragraph 1.3.2). Finally, real word use cases were shown, to better understand the practice of a real development of mHealth-centred platform for RWD collection, that will be faced in the next chapter.

2 SynCare: An Innovative Real-World Data System Secured by Cryptography and Blockchain

This chapter will describe the entire process, from the design to the development, of a RWD mobile-based ecosystem developed within this PhD research - the SynCare platform, a mHealth-based system to collect and manage RWD, aiming to improve the quality of life of its end-users. The design, the tools, and the frameworks for this development were based upon the notions acquired from the review described in the previous chapter, trying to reach a certain level of quality that will be assessed by the end-users itself as described in the third chapter.

The different tools, frameworks and processes chosen to coherently develop a secure- and quality-based RWD mobile-based ecosystem will be here described as follows: Section 2.1 describes the context at the basis of the prototype design; Section 2.2 describes the works from which some of the platform's characteristics were inspired; Section 2.3 presents the first implemented version of the developed RWD mobile-based platform; Section 2.4 describes the last evolution of this system bringing to the actual second version.

Part of the content of this chapter is derived from the following publications:

- ***Pighini, Claudio*** *& Cesareo, Ambra & Migliavacca, Andrea & Accardo, Matilde & Guarneri, Maria. (2022). Re-hub-ILITY: A Personalized Home System and Virtual Coach to Support and Empower Elderly People with Chronic Conditions. 10.1007/978-981-16-2380-6_81 [42]*
- ***Pighini, Claudio*** *& Vezzoni, Alessio & Mainini, Simone & Migliavacca, Andrea & Montanari, Alessandro & Guarneri, Maria & Caiani, Enrico & Cesareo, Ambra. (2022). SynCare: An Innovative Remote Patient Monitoring System Secured by Cryptography and Blockchain. 10.1007/978-3-030-99100-5_7 [43]*
- *My master thesis at https://hdl.handle.net/10589/164863*

2.1. The Context

Data is the new gold: it is continuously collected and analyzed to derive information that companies and organization are willing to buy. Centralized organizations – both

public and private - collect huge amount of personal and sensitive information and individuals have little or no control over the data that are stored about them and their usage. There is, consequently, a growing public concern about user privacy. This also applies to health data and, even more, to patient-generated health data.

In recent years there has been the multiplication and spread of health mobile apps and wearable devices capable of measuring vital and physiological parameters, leading to a powerful flood of data, which can be used for medical issues, related research, and to improve the care paths. Also, the COVID-19 pandemic accelerated the rise of telemedicine, telehealth and health tele-monitoring services [44-46]. Healthcare professionals (HCP) started or increased the use of ICT, such as email, text messages and video technology, to communicate with patients, sending prescriptions, monitoring symptoms, and giving medical consultations. Due to the need to face the emergency, regulatory standards on ethics, privacy and data protection were temporarily relaxed to allow this shift to socially distanced care [47, 48]. Nevertheless, attention to personal, sensible data privacy and protection must be re-established and, in this context, methods and application to favour secure exchange of data between parties (e.g., patient, general practitioners, medical specialists, hospitals, therapists, etc.) are urgently needed.

In this field, the use of Blockchain technology can play a key role. Since it was originally introduced and applied to the financial field [49], blockchain technology has gained substantial attention, and the interest for its application in diverse fields has constantly increased. The working principle of the Blockchain can be explained using its original application field: Bitcoin transactions. Let's think to the Bitcoin Blockchain as an interconnected collection of digital wallets [50]. A hypothetic transaction of Bitcoins from wallet A to wallet B is simultaneously shared with all other wallets ('miners') in the underlying Bitcoin Blockchain, which uses a cryptographic algorithm to validate the transaction.

Once a transaction is validated –which depends on chosen type of blockchain [51]- by a certain number of miners, it is stored in a block, which contains the details of the transactions (e.g., transferred sum, ownership, etc.), and marked with a time stamp and a cryptographic hash (a mathematically generated alphanumeric string) of the data. This block is added to the end of the blockchain, which is followed by the transfer of assets (e.g., bitcoins) to the receiving party. The cryptographic hash plays a crucial role in the blockchain mechanism because it permits to create a distinct, digital signature that is unique to the current block of data and, at the same time, it is created starting from the hash of the previous block, defining a secure link between consecutive blocks (a chain). Thanks to this mechanism malicious changes are prevented from being made to the blockchain ledger and the information related to all previous transactions are completely transparent [50, 52].

Figure 16 presents an example of how the Bitcoin's blockchain transactions work. As described in [54], "*Bitcoins are recorded as transactions. For instance, some user Charlie does not simply "hold" three bitcoins. Rather, Charlie participates in a publicly verifiable transaction showing that he received three bitcoins from Bob. Charlie was able to verify that Bob could make that payment because there was a prior transaction in which Bob received three bitcoins* from *Alice and there was no prior transaction in which Bob spent these three bitcoins.* ". Indeed "*each individual bitcoin can readily be traced back through all transactions in which it was used, and thus to the start of its circulation. All Bitcoin transactions are readable by everyone in records stored in a widely replicated data structure. In general, transactions are ordered recursively by having the input of a transaction (roughly, the source of funds) refer to the output of a previous transaction. (For example, the transaction might reveal that Bob pays Charlie using bitcoin he received from Alice.)*". Continuing the explanation of [52], "*Bitcoin relies on two fundamental technologies from cryptography: public-private key cryptography to store and spend money; and cryptographic validation of transactions. Standard public-private key cryptography lets anyone create a public key and an associated private key (Diffie and Hellman 1976). Public keys are designed to be widely shared—hence the name. Messages encrypted with a public key can only be descrambled by someone who possesses the corresponding private key, allowing anyone to encrypt a message that only the specified recipient can read. Similarly, messages encrypted with a private key can only be descrambled with the corresponding public key, allowing a specified sender to create a message that can be confirmed to be authentic. Public-private key cryptography is widely used: in the best-known example, web browsers on a HTTPS "secure website" encrypt communications with that site's advertised public key in order to begin a secure connection. In Bitcoin, similar encryption fundamentals authenticate instructions to transfer money to other participants. Such an instruction is encrypted using the sender's private key, confirming for everyone that the instruction in fact came from the sender.*". Thus, the example said "*Suppose that Alice has three bitcoins that she wants to give to Bob. She publishes a message in the Bitcoin network indicating that she is transferring three of her existing bitcoins, along with a reference to the transaction where she had received those bitcoins. Part of this message is encrypted by Alice's private key to prove that the instruction came from her, in a method akin to a signature on a paper check. Later, if Bob wants to send bitcoins to Charlie, he publishes a message, again encrypted with his private key, indicating that he got his bitcoins from Alice and what he wants to send to whom. The Bitcoin network identifies Alice, Bob, and Charlie only by their public keys, which serve as account numbers. Every new transaction that is published to the Bitcoin network is periodically grouped together in a "block" of recent transactions. To make sure no unauthorized transactions have been inserted, the block itself is compared to the most recently published block—yielding a linked sequence of blocks, or "block chain." A new block is added to the chain roughly every ten minutes. With this data structure in place, any Bitcoin user can verify that a prior transaction did in fact occur. Keeping the transaction record operational and updated is a public good, as it is the foundation of the entire Bitcoin system. To encourage users*

to assist, the Bitcoin system periodically awards newly minted bitcoins to the user who solves a mathematical puzzle that is based on the pre-existing contents of the block (which prevents tampering with the block and hence modifying prior transactions) and which can only be solved by computationally intensive methods that include a random component. Thus, faster computing is more likely to solve a given problem and will solve a greater number of these problems, but speed alone will not guarantee success. Upon solving the puzzle, the user publishes a "block" which contains a proof-of-work that a solution was carried out along with all observed transactions that have taken place since the last puzzle solution was announced and a reference to the previous complete block. After other users verify the solution, they start working on a new block containing new outstanding transactions. This process is called "mining" and recursively ensures that the total historical ordering on all blocks ("chain") is agreed by the entire network. A Bitcoin transaction does not clear (and hence is not final) until it has been added to the consensus block chain. Transaction batches are added every ten minutes on average. However, miners are continuously working on adding blocks of transactions and building on previous transactions. By continually presenting their solutions to the puzzles, with the associated new tail of the block chain, miners are in effect "voting" on the correct record of Bitcoin transactions, and in that way verifying the transactions. In some cases, a transaction batch will be added to the block chain, but then a few minutes later it will be altered because a majority of miners reached a different solution. Sources typically recommend considering a Bitcoin transaction final only after six confirmations, to assure that the transaction is truly recorded in a permanent part of the block chain. While this provides greater assurance, it creates a delay of approximately one hour before a Bitcoin transaction is finally validated."

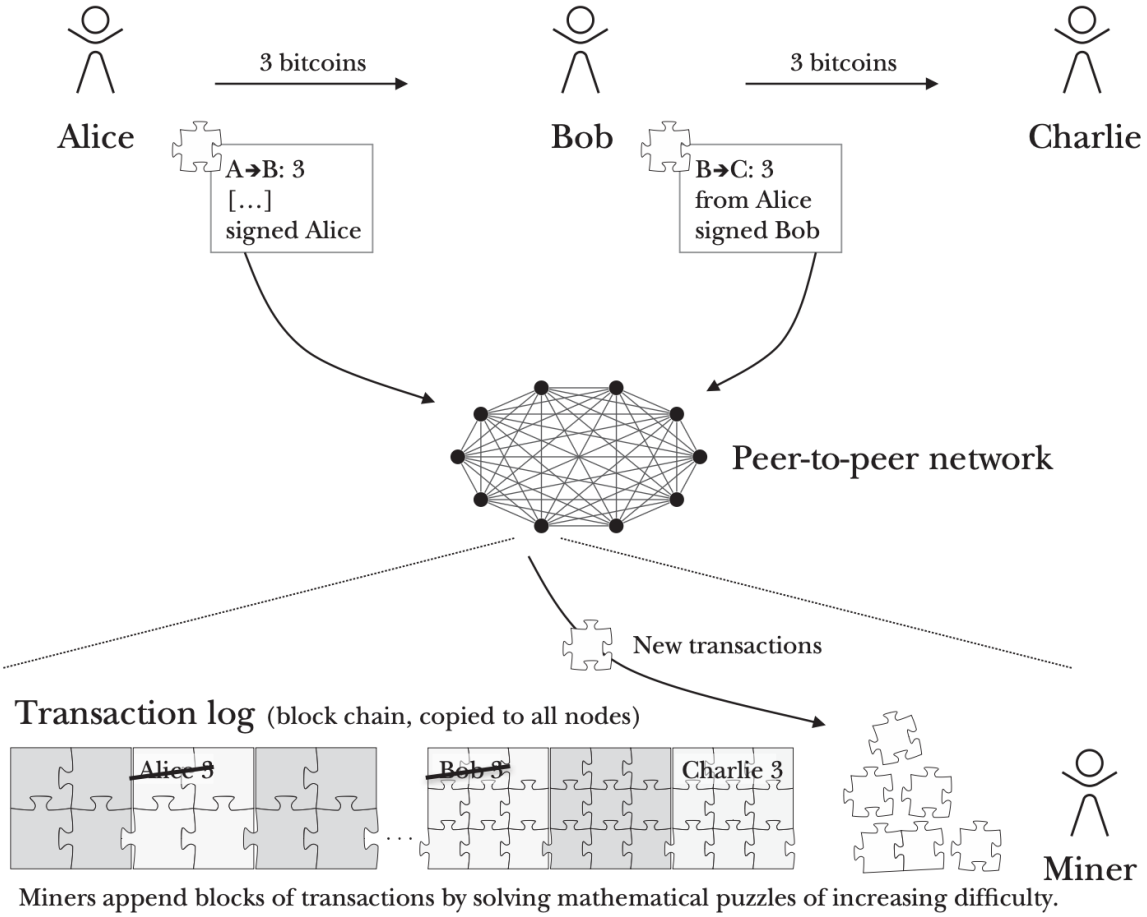

Figure 16: Bitcoin's Approach to Transaction Flow and Validation [54]

Now, let's change the digital asset of the example and consider performing transaction of data. Blockchain offers various application possibilities, ranging from management of Electronic Medical Records (EMRs) to Remote Patient Monitoring (RPM) solutions.

This chapter presents SynCare, a user-centric, secure system for health-related data recording and remote patient monitoring, focusing on the methods and solutions we developed and applied to allows safe exchange of data between patients and healthcare professionals, and to manage data sharing consents by using smart contracts registered on blockchain. The next paragraph "Inspirational works" will discuss the existing literature related to this topic, considering the most common applications of blockchain in healthcare.

2.2. Inspirational Works

Among the biomedical/health care applications of blockchain technology, one of the most popular is the management of EMRs [53]. Healthcare in fact suffers from a "data

silos" problem. Patients leave data scattered across various jurisdictions, moving from one provider's data silo to another. This has consequences not only for the patient, that lose easy access to past data and can interact with them in a broken manner, but also for organizations interested in using AI technology applied to large amount of labelled clinical data from many sources, to improve patient care and help clinicians.

The aim of applying blockchain-based technology in this case is to build a decentralized database management system where hospitals, providers, patients, and other relevant parties can store, share, exchange, and analyze data. One implementation example is Guardtime [54], a Netherland-based data security firm, which provided a blockchain-based system which links EHR data of patients with their blockchain-based identities. This system has been used in Estonia to secure 1 million health records.

Another known implementation is MedRec project [55]. Medication Reconciliation is a structured process in which Healthcare Providers partner with patients and their family/caregivers to obtain a complete and accurate, up-to-date list of the patient's medications which is then reconciled with admission, transfer and discharge orders. Blockchain implementation in MedRec project tried to facilitate this process moving from a slow access to fragmented medical data managed by healthcare providers to a system based on a decentralized approach to managing permissions, authorization, and data sharing between healthcare systems, based on patient agency. Via smart contracts on an Ethereum blockchain, MedRec allows to log patient-provider relationships that associate a medical record with viewing permissions and data retrieval instructions for execution on external databases. Using this mechanism, providers can add a new record associated with a particular patient, and patients can authorize sharing of records between providers. This approach allows patients to know and decide who can access their healthcare data, acquire copies of their healthcare records or transferring them to another healthcare provider. Although it has been only tested as a proof of concept with medication data, MedRec demonstrated how biomedical and clinical research outcomes may significantly benefit from the application of blockchain to provide rapid, secure access to longitudinal research data.

Other examples of application of blockchain in the field of EMR management tried to address the limitations of this approach, namely lack of interoperability among different blockchain-based EMR solutions (lack of standard), scalability (high volume of clinical data), data security and privacy [56-68].

Another use case involves the application of blockchain technology to facilitate remote patient monitoring (RPM) [53]. RPM involves the collection of patient-generated health data, using sensors/devices and mobile apps, to allow remote monitoring of patient's health status, also outside the healthcare environments. The aim in this field is to facilitate patient-centric data storing, sharing and retrieving, in agreement with the European General Data Protection Regulation (GDPR) which prohibits the

processing of sensitive personal data of patients unless explicit consent is given by the patients. In a recent work, Yue et al. [69] proposed an App architecture which allows patient to own, control and share their own data easily and securely by using blockchain technology.

Healthbank is a Swiss digital health startup which offers its users a platform on which users can store and manage their health information in a secure environment [70, 71]. The data sovereignty lies fully in the hands of the user. As a next step, Healthbank plans to consistently apply and implement Blockchain technology for the underlying business model. Using a private blockchain based on the Ethereum protocol, Griggs et al. created a system where the sensors communicate with a smart device that calls smart contracts and writes records of all events on the blockchain [72]. In another work, Liang et al. [73] proposed a mobile, patient-centered, blockchain-based system for personal health data sharing. This system is as a permissioned, private blockchain network developed on IBM Blockchain's Hyperledger Fabric. Similar solutions were applied for diabetic patients' monitoring [74] and cognitive behavioural therapy for insomnia [75]. Uddin et al. proposed a system for continuous RPM [76] and data sharing based on blockchain and end-to-end architecture.

2.3. SynCare Ecosystem Version 1.0

2.3.1. System Design

SynCare is a patient-centered ecosystem for RPM designed and developed through this PhD executive research by LifeCharger srl, with the aim to: 1) facilitate patient's self-monitoring and remote patient monitoring in chronic diseases, 2) support therapeutic alliance between patients and HPs and, 3) improve patients' engagement and therapeutic adherence for chronic patients or patients performing at-home therapies. To do this, it is extremely important to maintain a constant link between patients, healthcare professionals and informal caregivers.

The main goals for such an ecosystem should be to:

1. build up secure channels for data sharing, in compliance with GDPR
2. support the patients in the management of their own health data
3. clearly define the digital health services, circumscribing the doctor-patient relationship. This is fundamental to guarantee to the healthcare professional the possibility to report the services provided, referring to specific tariffs, also defining the responsibilities connected to these services.
4. as LifeCharger srl, to provide the above-mentioned services/ecosystem for the subscribed end-users, acting as a normal third party, without the need to view users' data without a user explicit consent.

Therefore, access to patients' data will be regulated through the creation of informed digital consents to clearly circumscribe a digital medical service. These informed digital consents must be traceable, transparent, and not tampered with, but must be withdrawable, in compliance with GDPR.

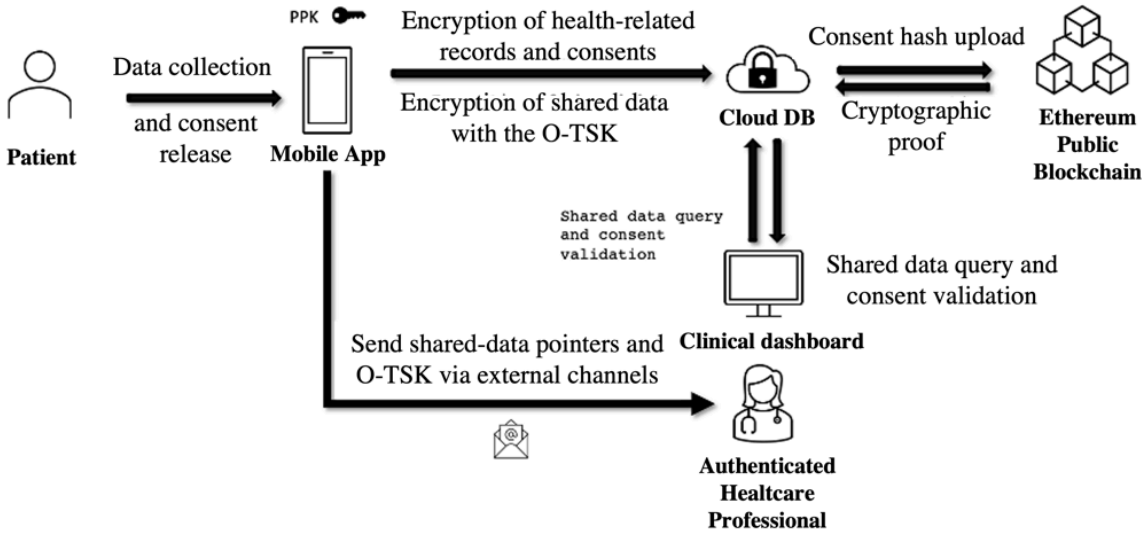

Figure 17: Architecture and Components of first SynCare Ecosystem version

The main components of the proposed SynCare ecosystem are the following (Figure 17):

- mobile app for the patient
- database on Cloud, storing all the encrypted, sensitive health-data
- public Ethereum blockchain to validate the data sharing consents
- dashboard for the healthcare professionals

The mobile app offers different features to patients; among others:

1. notifications to remind of drugs' intake or activities to perform,
2. a virtual diary to record and report symptoms, measurements of physiologic parameter, performed activities, visits and exams,
3. digital questionnaires,
4. medical reports manager,
5. management of online prescriptions, exams and visits reservation, drug ordering.

All the data that are inserted and managed by the app are locally encrypted and then uploaded to a Cloud DB. Data can be subsequently decrypted and visualized only by the patient by using a private key saved on the smartphone. The patient can decide to share such data with third parties, such as a healthcare professional or an informal caregiver, signing a digital data sharing consent through the mobile app.

This process can be applied to different use cases, ranging from remote patient monitoring and telemedicine to participation in research experimentations. To ensure that patients can be confident about the signed consent is the one they agreed to use and hasn't been tampered with, our solution uses smart contracts as a ledger of the signed sharing consents.

A smart contract is a transaction protocol stored in a blockchain, which is intended to automatically execute, control or document legally relevant events and actions according to the terms of a contract or an agreement, without any trusted intermediary's involvement or time loss. Because smart contracts are digital and automated, there's no paperwork to process and no time spent reconciling errors that often result from manually filling in documents. Moreover, considered that there's no third party involved, and the encrypted records of transactions are shared across participants, there's no need to question whether information has been altered for personal benefit.

Finally, blockchain transaction records are encrypted, which makes them very hard to hack. Also, given that each record is connected to the previous and subsequent records on a distributed ledger, hackers would have to alter the entire chain to change a single record. The blockchain gives an objective proof of the timestamp at which the consent was released. Indeed, the blockchain reduces the risk that the timestamp associated to the consent could be manipulated during the signature by an eventual intruding attacker that could get hold of the mobile app's code source.

Once the consent is signed by the patient and uploaded on the blockchain, data can be shared, being encrypted and left securely "off-chain", validated and visualized by means of a clinical dashboard built as a web app. This design ensures patients have the full control over their own health data and can decide who have access and how they are used.

2.3.2. Tools and Process for Development

2.3.2.1. Tools for Android Mobile App

An integrated development environment (IDE) is defined as "… a software application that provides comprehensive facilities to computer programmers for software development. An IDE normally consists of at least a source code editor, build automation tools, and a debugger." (https://en.wikipedia.org/wiki/Integrated_development_environment), and the choice of the IDE strictly depends on the operating system running on the smartphone, and on the IDE it-self (graphics, usability, etc…).

For the Android mobile app development, "Android Studio" (Figure 18) was chosen. This is the official integrated development environment (IDE) for Google's Android

operating system, built on JetBrains' IntelliJ IDEA software and designed specifically for Android development. The Android IDE presents embedded features useful for the development of smartphone applications, for example to automatically build the projects (the Gradle), to run or debug the apps on a virtual smartphone (Android Virtual Device Emulator) or the built-in support for Google Cloud Platform, enabling integration with Firebase Cloud Messaging. The standard programming languages are all supported, but typically the most used is Java, because it derives from IntelliJ IDEA, which is a Java integrated development environment.

The Android IDE needs the integration of the Java Development Kit (JDK), which is a software development kit (SDK), i.e. a collection of tools in one installable package that makes easier the app development by having a compiler, a debugger or sometimes a software framework. Android Studio is freely available on the official developer Android website (https://developer.android.com/studio).

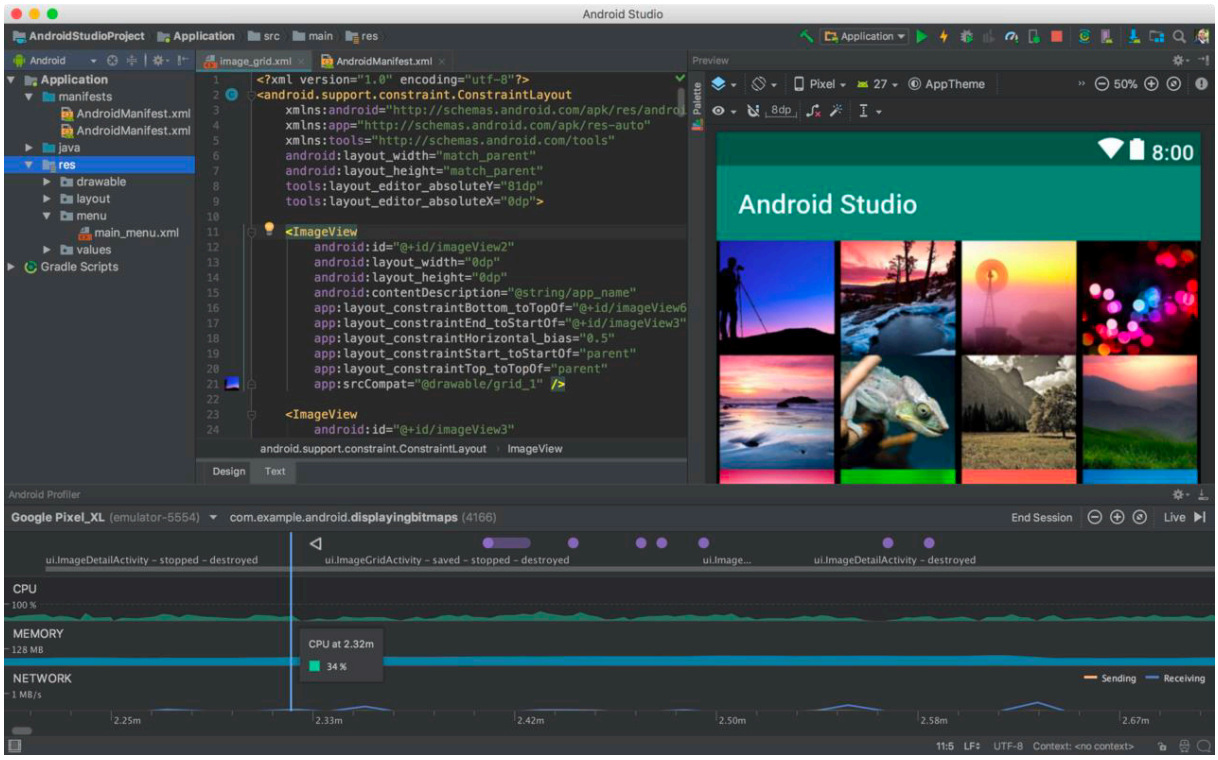

Figure 18: Android Studio official IDE screenshot (https://hdl.handle.net/10589/164863)

2.3.2.2. Tools for iOS Mobile App

For the iOS mobile app development, "Xcode" (Figure 19) was chosen. Xcode is the official IDE provided by Apple for building applications on iOS, iPadOS, macOS, watchOS, and tvOS. The IDE integrates all the essential tools for app development, including a graphical interface editor (Interface Builder), a code editor with advanced features such as syntax highlighting and auto-completion, and a powerful debugger.

Xcode also provides a built-in iOS Simulator, which allows developers to test and debug applications on virtual devices that reproduce the behaviour of real iPhones and iPads. The most used programming language is Swift, although Objective-C is still supported for legacy projects. Xcode includes the necessary software development kits (SDKs) and build system, making it possible to compile, test, and deploy apps directly to Apple devices or to the App Store. The IDE is freely available on the Mac App Store (https://developer.apple.com/xcode/).

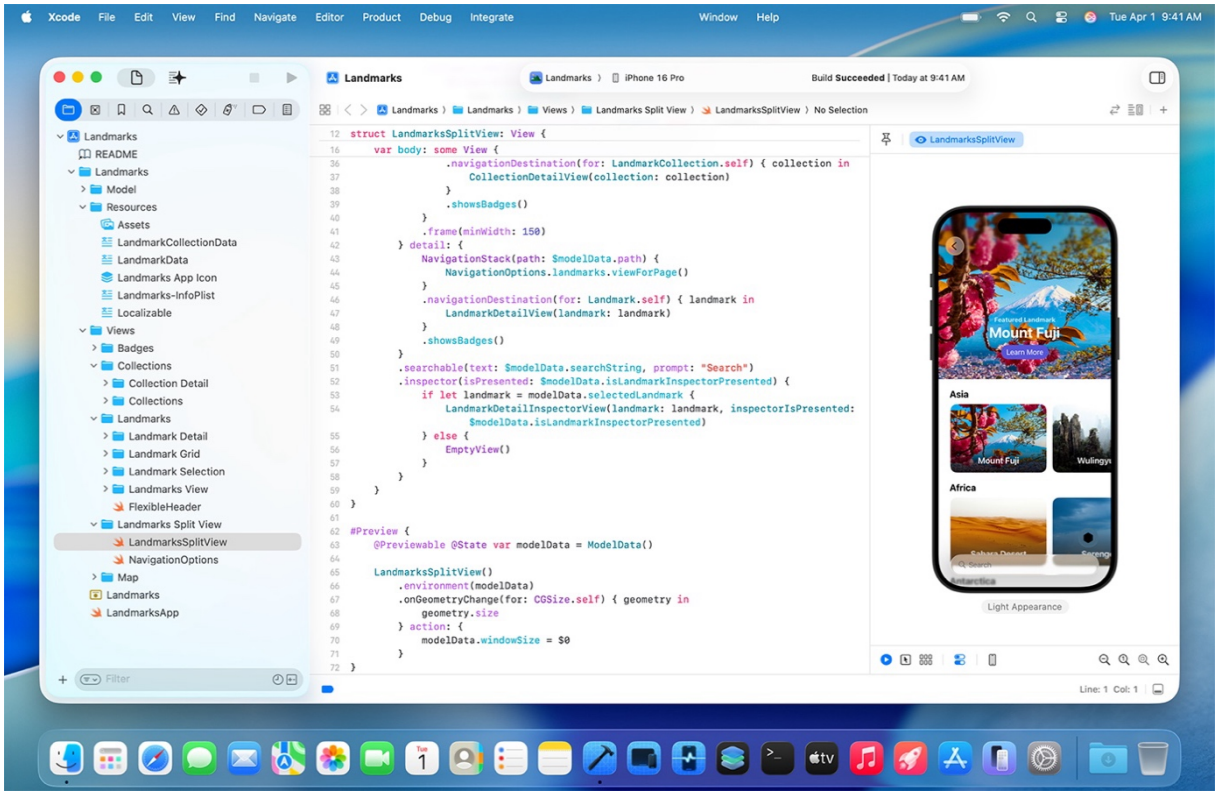

Figure 19: Apple official IDE xCode (https://developer.apple.com/xcode/)

2.3.2.3. Tools for Clinical Dashboard

For the development of the clinical dashboard, the IDE "Apache NetBeans" (Figure 20) was chosen. This is an official IDE for Java and other programming languages, maintained as an open-source project under the Apache Software Foundation. The IDE integrates features useful for enterprise web application development, such as code completion, project templates, refactoring tools, and direct deployment to web servers. In this project, the front-end of the dashboard was developed using HyperText Markup Language (HTML) and JavaScript inside JSP (JavaServer Pages) files, while the back-end was programmed in Java, relying on Apache Tomcat as the web server

to manage the servlets. Tomcat provides a robust and scalable environment to execute Java code on the server side and render the dynamic content through JSP, enabling interactive dashboards and secure data management. Apache NetBeans natively supports integration with Tomcat, offering tools to configure, run, and debug applications directly from the IDE. The IDE is freely available on the official Apache NetBeans website (https://netbeans.apache.org/), while Apache Tomcat is distributed by the Apache Software Foundation as well (https://tomcat.apache.org/).

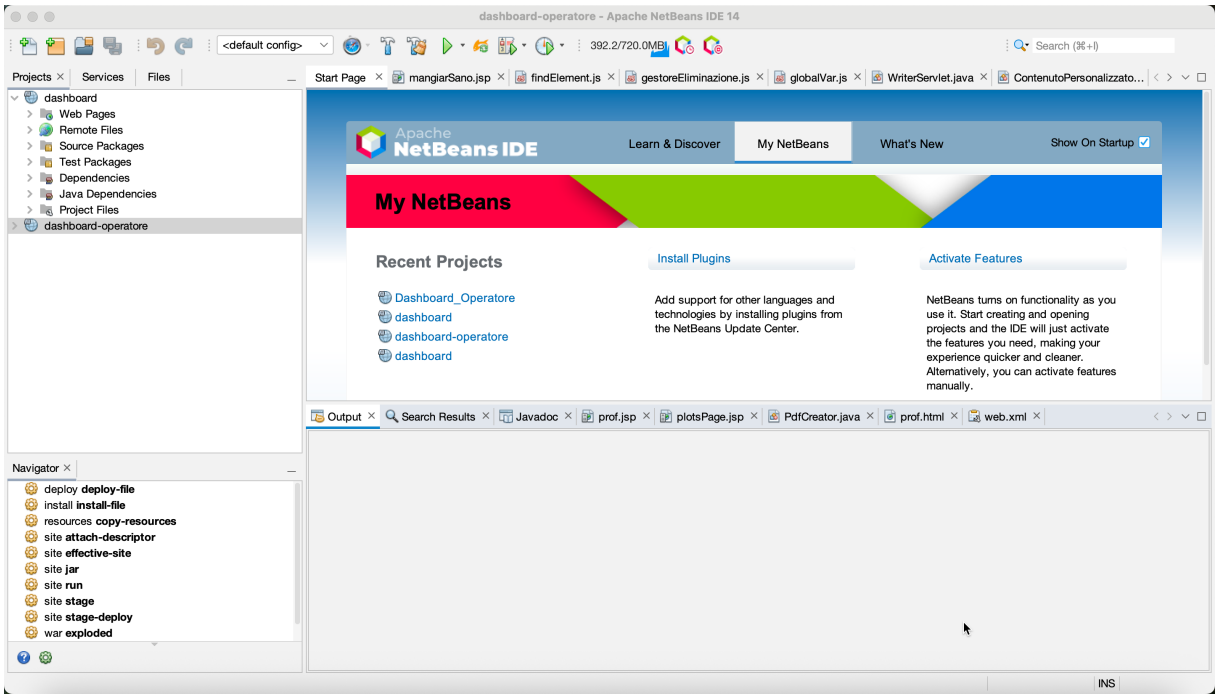

Figure 20: Apache Netbeans IDE screenshot

2.3.2.4. Environments and Versioning Control for App Development

For the development process, the workflow was divided into three separate environments: development, pre-production, and production, both for the front-end and for the back-end of the mobile apps and the clinical dashboard. For the back-end, this was achieved by relying on MongoDB Atlas as the data storage system and on MongoDB Atlas App Services as the back-end framework. MongoDB Atlas is a fully managed cloud database service for MongoDB, designed to simplify database deployment, scaling, and operations, while ensuring high availability and security (https://www.mongodb.com/atlas). Within Atlas, a cluster is a set of managed MongoDB servers that host the database, automatically handling replication, scaling, and backups. The back-end logic and integration with the mobile apps were implemented through App Services, which provide serverless functions, triggers, and APIs directly connected to the database (https://www.mongodb.com/docs/atlas/app-

services/). To enforce the separation of environments, three independent projects were created, each with its own cluster and corresponding back-end services (development, pre-production, and production).

The control and management of these environments, as well as their versioning, was ensured through integration with GitHub, a widely used version control system that allows developers to track changes to the source code, collaborate asynchronously, and manage different branches of a project securely (https://docs.github.com/en/get-started/using-git/about-git). In the same way, the differentiation and versioning of the front-end was managed by connecting the mobile app IDEs (Android Studio and Xcode) to the GitHub repositories, ensuring synchronized and controlled updates across all environments.

Thus, following a sort of agile process [10], the development phase was conducted safely and independently from the production environment, drastically reducing risks that could compromise live systems. The pre-production stage was used as a mirror of the production environment, enabling strong testing on realistic data before releasing updates into production (Figure 21).

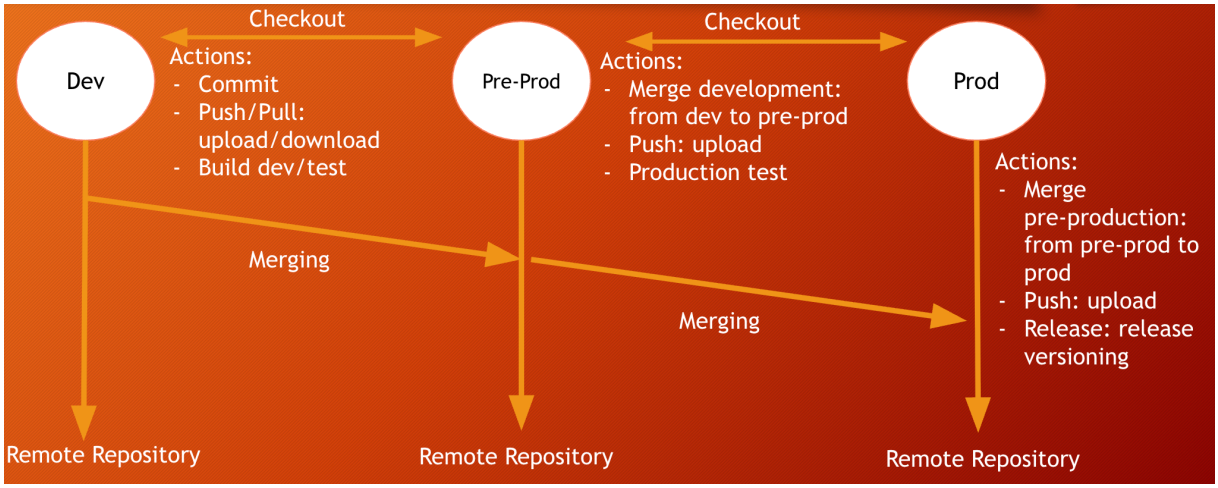

Figure 21: environment differentiations and versioning control from dev (development) to pre-prod (pre-production), to prod (production), with the different Github actions (checkout, push, pull, and merge)

2.3.2.5. Solidity for Ethereum Smart Contract

For the development of decentralized applications on the Ethereum public blockchain, "Solidity" is the official high-level, contract-oriented programming language designed specifically for writing smart contracts on Ethereum. A smart contract is a self-executing program deployed on the blockchain that automatically enforces the terms

of an agreement, enabling trustless transactions without intermediaries. Solidity presents embedded features useful for blockchain development, such as strong typing, inheritance, and libraries, which simplify the creation of reusable and secure components. The language is influenced by JavaScript, Python, and C++, making it accessible for developers with previous programming experience. Once written, smart contracts in Solidity are compiled into Ethereum Virtual Machine (EVM) bytecode, which runs on every Ethereum node, ensuring consensus and immutability. Solidity is open source and fully documented on the official Solidity developer website (https://docs.soliditylang.org/) and the Ethereum Foundation documentation (https://ethereum.org/en/developers/docs/smart-contracts/).

2.3.3. System Implementation

This chapter will focus on the data-sharing methods implemented within SynCare ecosystem, describing how security and privacy issues have been handled using robust data-encryption, and smart contracts on blockchain.

2.3.3.1. Overall Flow

At the first run, the mobile app generates a Patient Private Key (PPK), saved inside the secure app local storage. The PPK is composed by a Rivest, Shamir e Adleman (RSA)-key pair used to sign the consents and to encrypt an Advanced Encryption Standard (AES) secret key. When the patient inserts data within the app, these are encrypted using a One-Time Secret Key (O-TSK), which in turn, is encrypted with an AES encryption algorithm by using the local PPK. The encrypted data, together with the encrypted O-TSK, are then uploaded on the Cloud database, creating the secure health record. The data are saved on the Cloud and not on the smartphone for different reasons: 1) ensuring a light app memory, 2) saving space during data sharing (creating the shared data packet and sending procedure), 3) have a data backup in case the phone is lost by the user.

Through this mechanism, the patient is thus the only actor which can decrypt and visualize its own data using the PPK locally stored on his/her personal device.

Whenever the patient signs a specific digital consent to share the data with a third party, the mobile app will automatically create the cryptographic hash of the signed consent, feeding the hash-generating function with the consent meta-data, and then upload it to the cloud DB. Subsequently, an asynchronous cloud server service will feed a Merkle Tree algorithm with the calculated consent hashes to generate the root hash and the cryptographic proof. This algorithm ascends the tree generating a path hash from each couple of leaves until the root is reached, creating the root hash. The hashes of each path are saved inside the cloud DB, associated with their consent hash, while the root hash is stored inside a smart contract deployed on the public Ethereum blockchain.

Once the consent is signed the data sharing can be triggered; specific functions of the mobile App will 1) query the Cloud DB to find the data specified by the consent, 2) decrypt them on the patient's device, 3) generate a O-TSK, 4) encrypt them again with the O-TSK, and finally 5) upload the new encrypted data (shared data) on the Cloud DB. The O-TSK is concatenated with the pointer to the shared data and sent through external channels (e.g., by email) to the third party. The O-TSK will be used by the third party to decrypt the patient's shared data. Healthcare professionals are provided with a web app which acts as a clinical dashboard, allowing an intuitive and compact visualization and representation of the shared data, and more importantly, verifying their coherence with what has been specified in the sharing consent signed by the patient.

Every time the patients insert or update their health data inside the mobile app, the latter controls if the data are linked to a signed consent. In the positive case, the app automatically updates the shared data pointed by that consent, allowing the healthcare professional web app to query each time trustable and updated patient health-related data.

2.3.3.2. The Mobile App

Initial Setup

As anticipated in the previous paragraph, at the first run an initial setup procedure on the mobile app generates the PPK, thus, the RSA private (PvK) / public key (PbK) pair, and an AES 256-bit secret key. The PPK is stored in a secure location, corresponding to the KeyStore on the Android operating system and the KeyChain for the iOS. These are two solutions offered by Google and Apple to memorize private information and lowering the risk of data breach in the case of smartphone hacking.

Once the user has been registered on the mobile app, the SynCare ecosystem associates the user's PBK to his/her public information, such as the email and the user ID. For this reason, every time the user logs in on the app the system checks if the PPK has changed, whether it is due to the change of the device or the deletion of the app. To avoid loss of data in the case of device change or app deletion, and to ensure continuity of use for the users, a backup function has been included, allowing the user to save the PPK encrypted into the cloud DB, and consequently allows its retrieval in case of loss.

The initial setup procedure also includes the signature of an umbrella consent to share data (see next "digital sharing consents" paragraph).

Scheduling

Once the initialization is concluded, the user can start to schedule the activities that are prescribed into the therapy or, if the context provides for it, will receive a machine-

readable, structured care plan which specific apps' functions will turn into scheduled activities.

The user can choose among different types of activity and schedule them following the guided procedure offered by the app (Figure 22).

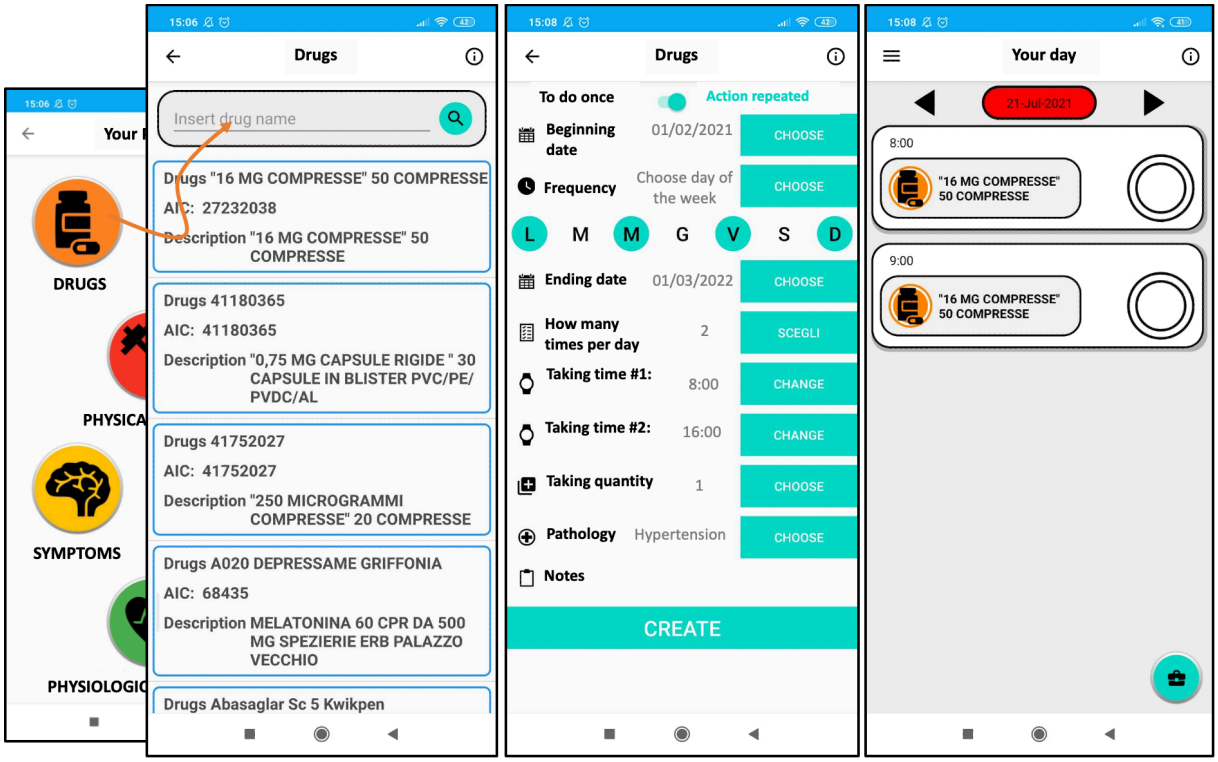

Figure 22: scheduling process of the mobile app

Every time an activity is scheduled, the app performs the following steps: 1) encodes the scheduling information following a JSON structure; 2) generates a 256-bit AES key for the symmetric encryption algorithm; 3) encrypts the JSON data structure with the AES key using AES-GCM, 4) encrypts in turn the AES key with the user PbK.

After these operations, a private packet is created with these two components: 1) the AES symmetric key encrypted with the RSA PbK, and 2) the JSON containing the information to be stored, encrypted with the AES symmetric key. This packet is securely saved inside the cloud DB.

On the opposite, when the app needs to retrieve the user information to be visualized on the smartphone, the performed steps will be the following: 1) the app asks the LifeCharger cloud DB for the private packet ID; 2) the app uses the RSA PvK to decrypt the part of the packet containing the encrypted AES symmetric key, and 3) the AES symmetric key is used to decrypt the second part of the packet containing the encrypted JSON with the patient's scheduled activity information related to the

therapy. This implementation for data encryption/decryption ensures that the patient is the only one who has access and can visualize his/her own data.

Digital Sharing Consents

The SynCare platform has been designed to allow the mobile app to share the patient's health-related data only through the signing of digital sharing consents. Digital sharing consents are smart contracts registered on blockchain which allow to clearly define the contract between the patient, the informal or professional caregiver or the generic third party with whom the patient wants to share the data. The contract defines:

- Contractors: who owns the data and who can access them
- Type of data shared: it is possible to share one or more datatypes (drugs, symptoms, physiological parameters) or select data with specific tags (e.g., classified per pathology)
- Temporal limits: continuous sharing (real time monitoring), one-shot sharing (visit related sharing) or periodic sharing (monitoring)
- Finality for which the data are shared and linked data usage (this covers the definition of the legal responsibilities for the healthcare professional in case of medical services

Digital sharing consent can be classified into two main categories:

- Umbrella sharing consents: signed just once by the users, typically during the initial setup procedure. This kind of consents are mandatory; this means the user cannot use the app if he/she does not sign this kind of consent. One example of umbrella sharing consent is the one used for research projects, that authorizes LifeCharger srl or other partners of consortium research projects, to analyze the user data for statistical/research purposes or to share collected data with other companies/partners developing modules and components of the overall project platform. In this case the patient/subject who is enrolled in the research must give his/her consent for data sharing and processing, for the purposes and in the manner described in the consent, under penalty of non-participation in the project. Umbrella sharing consents are signed by the users by using the stored PvK.
- Specific sharing consents: these consents can be signed by the users, but the non-signature does not preclude the use of the app (see Figure 23). The user has an active role in this case because he/she decides to share the data collected through the mobile app with a third party, and to do it will sign a specific consent, which describes the kind of data to be shared, the time of sharing (start and end date), the actors involved (sender and recipient) and the finality of use of the data. This kind of consent is typical of the patient-caregiver relationship.

Once the patient has agreed to all consent policies, the app creates the signed consent record. Independently from the type of consent, this operation includes: 1) the calculation of a hash starting from the information described into the consent, thus the consent meta-data; 2) the creation of an unique ID that is assigned to the shared packet containing the shared data as UUID; 3) the calculation of the timestamp relative to the moment of consent signing; 4) application of a signature to the consent hash with the RSA PvK, in order to ensure that the data owner has done this operation. These data are added to the signed consent meta-data and saved encrypted into the cloud DB. As the user gave his consent for data sharing, the app will generate the packet that will contain the patient's data to be shared and described by the digital consent.

This operation includes: 1) the encoding of the information inside a JSON structure; 2) the creation of a hash of the JSON data; 3) recovery of the PbK and to the package; 4) concatenate the hash with the timestamp; 5) the system signs with the PvK the concatenated string; 6) the generation of a 256-bit AES key, the O-TSK, which is used to encrypt the JSON part containing the health-related data; 7), finally, the packet of data to be shared is created by combining the encrypted JSON and other transparent anonymous data regarding general info of the consent, thus, the shared packet is saved on SynCare cloud DB.

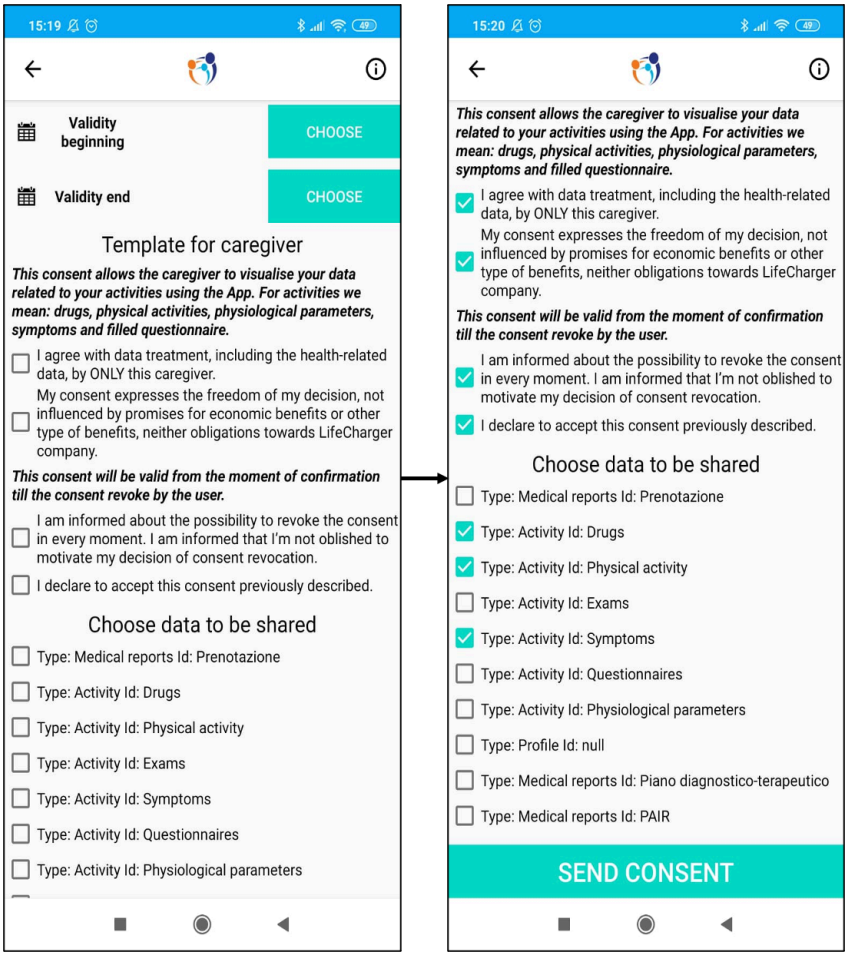

Figure 23: consent signing and sending procedure. The figure shows an example of a consent for an informal caregiver

Consent Withdrawal

In compliance with GDPR, our solution foresees the possibility for the patient to withdraw the consent at any time. To allow this, the system keeps track of all the shared data packet linked to each signed sharing consent. When a user decides to withdraw a previous consent, the linked shared data packets are delated from the DB and the corresponding hash marked as "not valid", thus the mobile app will stop to share the data packets related to that consent. This means that the linked viewership permissions are modified and the third parties which previously received the link with the O-TSK to decrypt the shared data will not be no longer able to retrieve those data packets.

The data sharing between the app's user and the third parties inside the SynCare ecosystem starts from the assumption that the shared data can be opened only via browser. Indeed, at the end of the data packet creation that contains the patient's

shared data, the app will generate a link that will be sent via a selected email client into the smartphone. The link il composed of the following parts:

1. the URL of LifeCharger srl https service that provides the clinical dashboard
2. the Universally Unique Identifier (UUID) that identifies the shared packet record, saved into the cloud DB, concatenated to the previous one (according to the syntax implemented by LifeCharger)
3. the "#" and a secret information (O-TSK) needed to recreate the symmetric key to decrypt the message.

This is an example of how the link looks like: https://share.lifecharger.ey/(UUID)#(SECRET).

By inserting the O-TSK after the "#", the server will not be able to read the secret key that is used to decrypt the shared data. Thus, LifeCharger acts as clearinghouse during the data sharing process, without the possibility of seeing the shared data among the user and the third parties.

USE CASE: Mario suffers from Parkinson and during his last visit, his neurologist, Dr. Moore suggested that he joins the continuity care program using the SynCare platform. Thus, Mario downloaded the mobile app as suggested by Dr. Moore and registered on it.

Subsequently Dr. Moore sent a sharing consent request via web Dashboard. In the request, Dr. Moore asks Mario to digitally sign an in-app consent that defines the relationship of the digital continuity care service: the consent defines that Dr. Moore will send a digital care plan that will be received and visualized by Mario through the mobile app as a structured agenda containing the assigned activities, and they will plan 5 video-visits in the next 12 months. Dr. Moore will monitor the trends and the care path of Mario to define the needed adjustments of the care plan; to do this, he needs to view data collected by Mario regarding the taken drugs, reported symptoms, vital signs, and questionnaires. The consent defines that these data will be accessible for Dr. Moore two days before and two days after the planned video-visits for a total period of 12 months.

Mario agrees to all consent policies, signing the consent. From this moment, all data types described by the consent will be encrypted and included in the shared data packet by the mobile app. Two days before the next video visits with Dr. Moore, the app will generate and share with him via email a link containing the pointers to the shared data packet and the key to decrypt the data. He will use this link pointing to the web dashboard, and after authentication with his credentials, he will have access to the data of Mario. Dr. Moore, according to the signed consent, will be able to access and view the data for two days after the visit, then the sharing data packets will be deleted and will be available again and updated with new data at the next visit.

Some weeks after starting using the mobile app, Mario decides to add his son Luca, as an informal caregiver, using the specific functionality of the app. To do this, he must sign another consent, specifying what types of data and how often to share with the child. He decides to share all data in a continuous way with Luca. So, this latter, using the reporting functionality of the app in caregiver mode can view all data regarding the health status and therapeutic path of the father, including pharmacological adherence and vital signs trends.

2.3.3.3. The Encrypted Cloud DB

The SynCare cloud DB relies on a non-relational database structure, where data are stored as simple key/value pairs. In particular, the structure of each record inside the SynCare cloud-based DB follows the typical structure of a JSON document.

In general, each record stored by the app is composed of a transparent unencrypted part, that represents the non-sensitive information (the user ID, a hexadecimal string that defines uniquely the patient inside the SynCare ecosystem, different timestamps, and reference keys linking to different collections) and an encrypted part, which encapsulates the obscured sensitive data.

From the previous paragraph, we can identify two types of data saved into the database by the app. The first one is represented by the information that only the user can read through the decryption procedure introduced in paragraph 2.3.3.2. The second one is the shared data packet that is stored on the cloud DB at the end of the data sharing procedure, waiting for the retrieval by a third party through the generated link, that is sent via email. In fact, the only way to open and visualize the patient's health-related sensitive data is to receive the mentioned link and, through the adopted web app (see paragraph 2.3.3.5), decrypt the patient's data. Consequently, neither the SynCare company owner, LifeCharger srl, nor a general third party, can access the sensitive part saved inside the records without the patient's authorization, given by signing a digital consent.

2.3.3.4. The Blockchain consent validation and synchronization

The SynCare ecosystem implements a software developed by LiberActa srl (LA) to upload the anonymous consent data on the Ethereum public blockchain. This software is based upon a cloud back-end that can interact through REST APIs and a smart contract deployed on the Ethereum blockchain.

This system aims to memorize on the Ethereum blockchain the past digital consent data signed through the mobile app. For this reason, the software was written to decouple the consent signing phase and the storage on the public blockchain. In particular, the consent data are passed to the LA back-end every time a consent is

signed by the mobile app. The consent data are initially saved only into the SynCare cloud DB.

Consequently, the LA back-end concatenates the received data inside a buffer. When the buffer maximum storage capacity or a certain established time are reached, a process is run to collect the unsaved consent data. This latter generates a Merkle Tree.

The root of the generated Merkle Tree is then saved inside each record of the previously processed consents, together with the cryptographic proof that allows the consent validation. Therefore, the root of the Merkle Tree is stored inside the smart contract, allowing a light transaction into the public blockchain.

At regular intervals, SynCare downloads the cryptographic proofs saved into the LA database, associating them to the relative consents. Thus, to verify the existence of a certain consent on the blockchain, SynCare can simply 1) calculate the consent hash, 2) reconstruct the Merkle Tree root with the provided cryptographic proof, and 3) verify the presence of that root using the smart contract. This process is executed automatically by the SynCare clinical dashboard, without the need for an active user interaction.

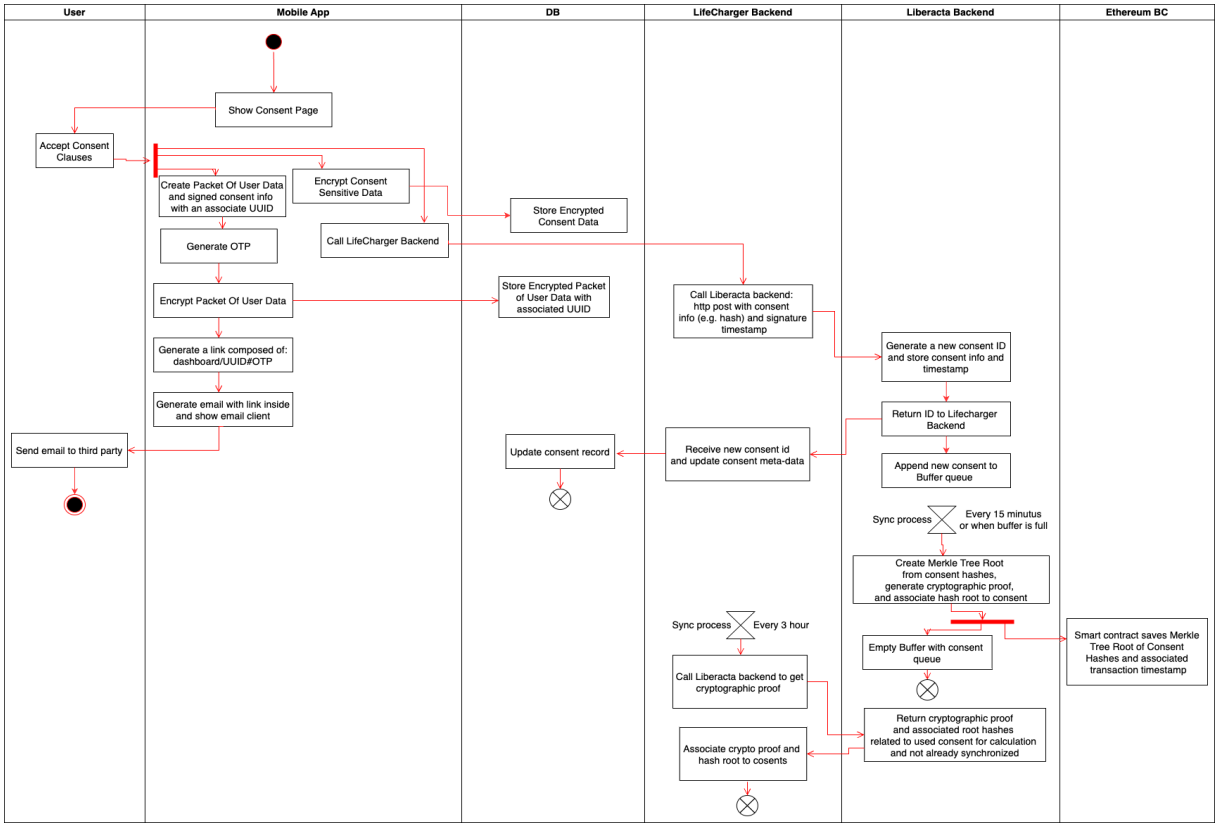

Figure 24: Innovative Smart Consent-Based Data Sharing Process, Data Encryption, and Blockchain Consent Data Synchronization (Activity Diagram)

2.3.3.5. The Clinical Dashboard

The clinical dashboard is a web application whose main purpose is to allow healthcare professionals to visualize the data collected by the patient through the mobile app, allowing to display and analyze the shared data. The Dashboard implements two key features that enforce the privacy and make the exchanges between the patient and the healthcare professional a sort of end-to-end encrypted channel. The first feature is the decryption performed on client side through Javascript code locally on the browser of the healthcare professional. The Dashboard retrieves the encrypted information from the Cloud DB. However, considered that the decryption key O-TSK is communicated by the patient by email or other means external to the SynCare platform and that the decryption is done on the browser, no sensitive information is exposed on the SynCare cloud infrastructure.

The other key feature provided by the Dashboard is a check, done on the client side through Javascript code, certifying that the information shared by the patient matches the consent previously signed. The encrypted shared data, in fact, contains a copy of the consent signed by the patient. It is worth noting that the consent is not just a pure text object but also contains a data structure, that is a formal description of the information that is going to be shared with the consent. It is a simple list of codes each one identifying a specific health information based on an agreed taxonomy.

The Dashboard performs the following checks: 1) the data shared by the patient must match with the data structure of the signed consent, 2) the consent must be signed by the same patient that encrypted the shared data, 3) the consent must have been registered in encrypted form by SynCare, and 4) the consent has been registered on the Blockchain.

The SynCare Ethereum Smart Contract doesn't expose sensitive data, in fact only the cryptographic proof of existence of the consent is tracked on the Blockchain. The Dashboard can check if this cryptographic proof matches with the specific consent and provides the corresponding Ethereum transaction ID, so the check can be done externally to SynCare. Eventual failures in the checks described above produce an alert on the Dashboard. A remarkable aspect of the Dashboard is that both the decryption and the compliance check between consent and shared data are done on client side, that is on the healthcare professional browser, so the users do not need to trust or rely on SynCare, and/or on the cloud application for these critical tasks. With this mechanism, the client can validate the consent data in automatic and transparent way.

As an additional safety measure the Dashboard needs the healthcare professional to be authenticated. This constraint does not invalidate the end-to-end encrypted channel described above but protects against malicious attempts to steal the decryption keys. In fact, intercepting the O-TSK sent to a healthcare professional without his/her

credentials would be useless. Moreover, considered that the system works based on sharing packets (shared data packet) each packet linked to a specific consent, is encrypted with a different O-TSK, therefore having the credentials to access the client and a link with the O-TSK, will allow the decryption of only the data packet specified in that specific consent.

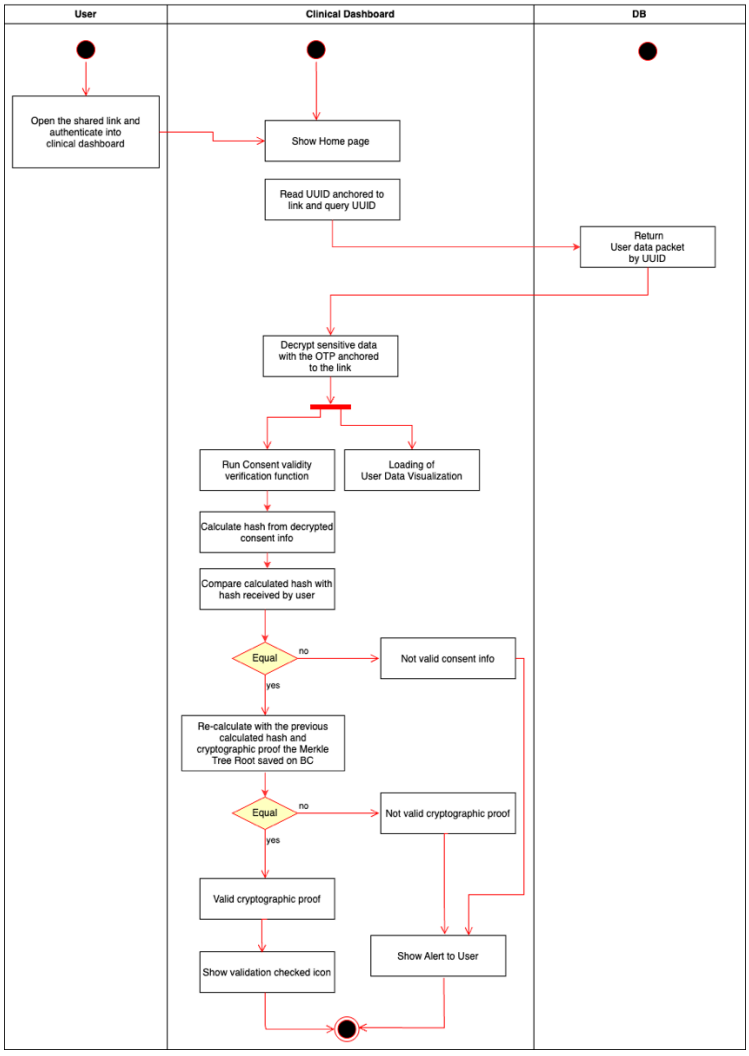

Figure 25: dashboard user's data decryption and consent validation (Activity Diagram)

2.3.4. Discussion and Conclusions

Scalability of blockchain-based healthcare solutions is a major challenge especially in relation to the volume of data involved. It is not optimal, or even practicable in some cases, to store the high-volume biomedical data on blockchain as this is bound to cause serious performance degradation [53]. To solve this problem, our solution uses a smart contract registered on a public blockchain as a ledger of the sharing consents signed by the patient. All the patient's sensitive data are left "off-chain" and opportunely

encrypted to be stored and shared. This solution allows fast and lightweight blockchain transactions, reducing the costs of each blockchain consent storage and simplifying the maintenance of the smart contract. Moreover, contrarily to the majority of the existing implementations in the same field that use private [55, 69, 73, 76] or semi-private [72] blockchains, our solution exploits the advantages of the public Ethereum blockchain, namely robustness and stability, without affecting privacy and data security, having the sensitive data saved encrypted off-chain. Moreover, in most of the solutions using private blockchain, data are saved not encrypted; this means that whoever has the access credentials can see private information of patients. As a final advantage of using a public Ethereum blockchain we mention the savings in maintenance costs.

For what concerns "off-chain" data security, our solution applies data encryption with AES using 256 bit one-time, disposable, secret key. This means that each time data is encrypted a new key is used; moreover, the private key saved on the user's smartphone is used to encrypt the secret key which has encrypted the data ensuring greater data security.

Considering the data sharing function, our solution puts the patient at the center of the process: in fact, the user decides which data to send by consent creation or acceptance of consent generated by a third party. The system has been designed in such a way that it is always the user that initializes the data sharing, in fact the created data package is linked to the consent for data sharing signed by the patient.

An important limitation in previous implementations is the limited speed of the blockchain-based transactions, which can introduce some significant latency. Our solution tries to reduce this problem allowing to create an asynchronous loading of consent data inside the public blockchain, decoupling the user experience from the blockchain interaction, which can be slow, without compromising the data security.

Moreover, by collecting all the consent data into the LA buffer and memorizing them as a Merkle Tree root, the cost of every transaction inside the blockchain is drastically reduced. The main limitation of the system regards the time of data encryption/decryption which, in the current version of the system, is performed each time the user opens the calendar function. This means long charging times when shifting from a function to another of the mobile app. This problem worsens increasing the amount of data inserted by the user.

To conclude, SynCare allows continuous and trustable patient remote monitoring, in compliance with privacy normative and leaving to patients the full control of data access permissions. Data sharing consents managed as smart contracts allow to clearly define which data are shared with the healthcare professionals, the temporal characteristics of the data-sharing (e.g., continuous, one-shot, starting and ending

dates), and how the data are used (which performance is expected). This is the first step for a clear definition of the medical performance in telemedicine, including responsibility and accountability, and could foster the spread of telemedicine and teleassistance services.

Next steps of development will focus on speeding up and optimizing the processes of encryption/decryption of data to ameliorate the user experience avoiding long charging time when opening the app and switching between app's functionalities. As already mentioned in the discussion, the latency introduced by encryption/decryption process is currently the main limitation of the system that worsen the user experience. To ameliorate this aspect, we introduced a local Realm on the smartphone, where a subset of useful data is saved unencrypted. As a future work, we plan to make specific performance tests to quantify the latency introduced by the blockchain-based transactions, including encryption/decryption phases. On the other hand, we are working on additional features: the first one regards the refinement of the consent management, introducing the fundamental possibility to modify and/or withdraw the consent, with consequent change of viewership permissions. Another improvement wants to take advantage of the use of blockchain to provide to the patient/user a log of all data accesses to the shared data. This would add transparency to patient-provider relationships while keeping participants informed and engaged in the evolution/use of their records. Finally, we plan to further increase the security of our solution, trying to minimize the possibility of external attacks aimed at manipulating the source code of the app. To do this we will perform a security analysis with an attacker model.

2.4. SynCare Ecosystem Version 2.0

LifeCharger (LC) SynCare 2.0 is no more only a patient monitoring platform, but a comprehensive ecosystem designed to strengthen the therapeutic alliance between professionals and users by delivering digital health and wellness services.

The LC SynCare ecosystem purposes are dependent on the specific application field in which it is deployed. For example, a psychologist could provide a service for remote psychological consultations and provide personalized mental wellbeing suggestions through the LC mobile App, that represents the patient's front-end, while a speech therapist could remotely provide speech training and prescribe different personalized exercises shown through the same app.

Indeed, the LC SynCare Ecosystem has been designed as a general-purpose platform acting as service delivery that can be specialized through the activation of different services, according to their different purposes. By performing the different prescribed activities (e.g., measure physiological parameter, fill-in questionnaires and evaluation scales, report symptoms, etc.), the patients allow the professionals linked to the services to monitor their performance and health status.

In this way, the LC SynCare ecosystem purpose relies on the activated services, that are the real products offered to the end-users, by monitoring how the user engaged with such services.

To allow the fruition of these services, the LC SynCare Ecosystem architecture relies basically on 3 levels, declined into 3 different software application:

1) the mobile App, that represents the end-user front-end and the patient's gate to the LC SynCare Ecosystem;

2) the Clinical Dashboard, that represents the professional front-end and the software to prescribe and monitor user activities;

3) the back-end, including the Data Analytics module, where the user data collected through the App are processed whose results will be shown on the Clinical Dashboard

The dataflow, described by the diagram of Figure 26, starts from the patient that collects data by using the LC App. If the patient signed the digital consents approving the data sharing with third parties (LifeCharger included), data can be shared by the LC App with the back-end for analysis. Every time a consent is signed, the relevant information is saved into the Ethereum Blockchain as a Smart Contract, thus allowing a transparent tracking of signed consents [43].

The Data Analytics module processes the data to be visualized by professionals through the Clinical Dashboard. Professionals can thus use the Clinical Dashboard to visualize the data of their patients, to monitor their situation and potentially send them feedback and action plan, thus closing the loop.

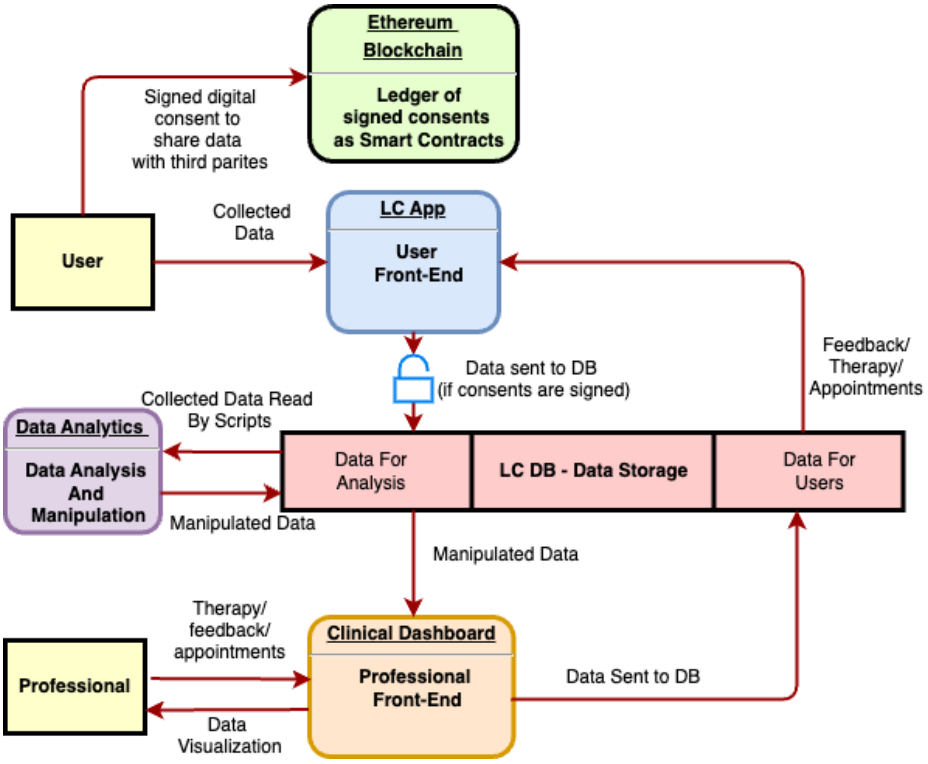

Figure 26: block diagram representing the data flow passing through the LifeCharger SynCare Ecosystem modules.

Moreover, the Data Analytics Module processes data also to provide direct reporting data to the user's app to monitor its adherence, app usage, and trends.

2.4.1. Architectural Differences from SynCare 1.0 to 2.0

The main difference passing from version 1.0 to 2.0 relies on the creation of Data Analytics module. Indeed, another depiction of the architecture can be offered by placing emphasis on the actors who interact with the system and by centralizing attention on the Data Center & Analytics modules as in Figure 27.

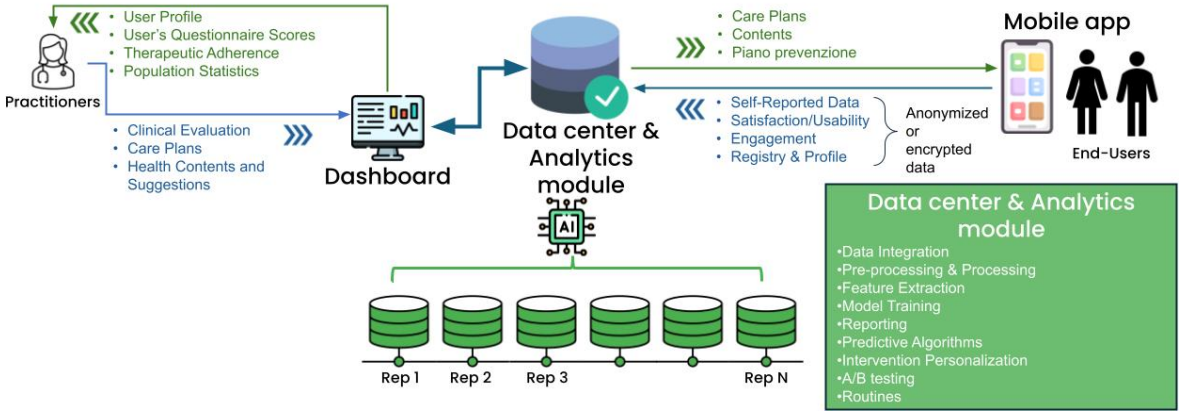

Figure 27: adaptation of the centralized architecture around the Data Center and Analytics modules

The "Data Center" module comprises the entirety of the repositories used to 1) store the raw data that will subsequently be processed by the "Data Analytics" module (shown in Figure 26 as the central "Data for Analysis" component), which is distinct from the "LC DB – Data Storage" block used to save the encrypted data consumed directly by the mobile and web applications; and 2) retain the outputs produced by the "Data Analytics" module, making them available for retrieval by the various front ends (mobile app and dashboard).

All data stored by the LC ecosystem in these repositories is maintained in a pseudo-anonymized form: a unique identifier code (generated by the mobile apps) replaces the user's personal identity, while the sensitive data fields remain encrypted in the cloud database. The sensitive part of user's meta-data is encrypted by the mobile apps using a unique public key generated for the entire environment (Figure 28).

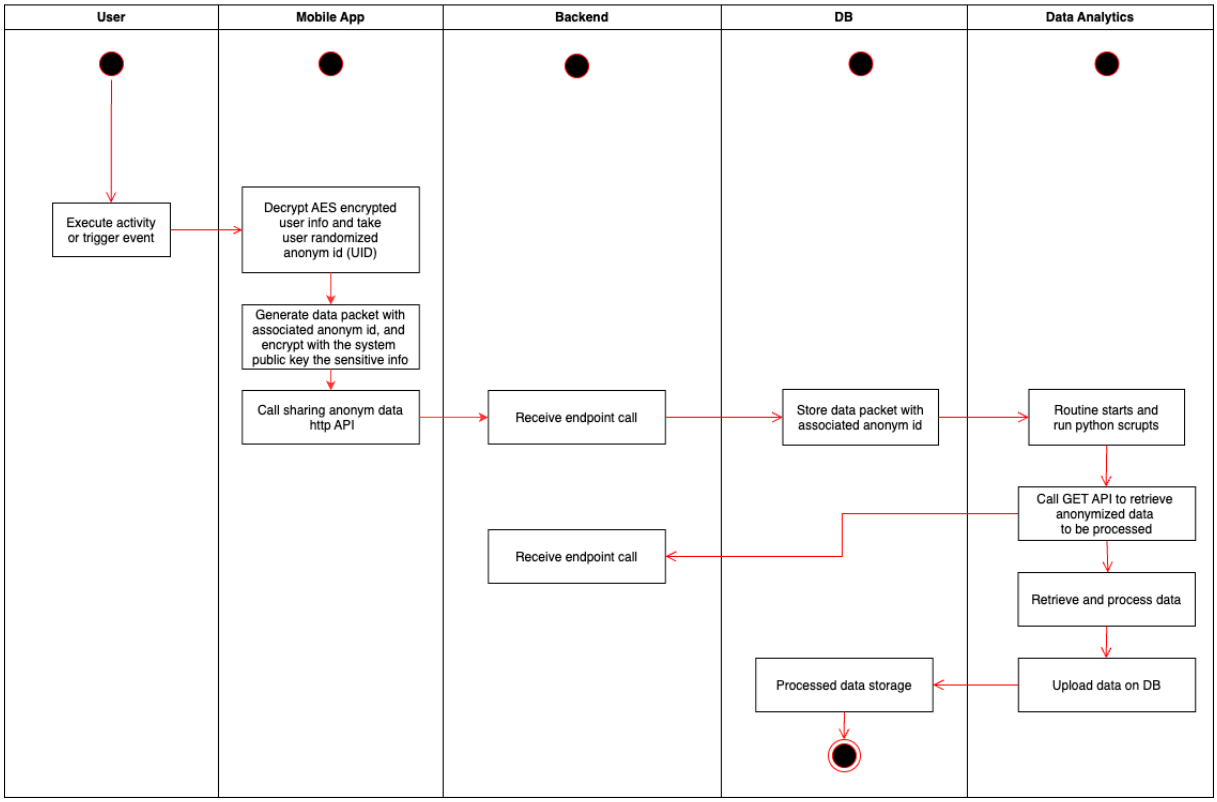

Figure 28: pseudo-anonymized data sharing, process and storage (Activity Diagram)

Thus, differently from the version 1.0, the pseudo-anonymized data are sent from the app to the repository for feeding the Data Analytics module, while the data sharing of the version 1.0 was direct from the app to the clinical dashboard, without any post-process. Indeed, a new clinical dashboard to allow the reading of those anonymized data was developed.

The clinical dashboard was implemented with a combination of Flask (https://flask.palletsprojects.com/en/stable/) and Dash Plotly (https://dash.plotly.com/), for the back-end and frontend frameworks, respectively, written in python programming language (https://docs.python.org/3/). The IDE chosen for this development was PyCharm Community Edition (https://www.jetbrains.com/pycharm/).

This new web app allows the practitioners/professionals to login, with username and password authentication (Figure 29), if and only if they own the unique environment private key that the dashboard will use to decrypt user's sensitive data, to allow the de-anonymization process (Figure 30), that were encrypted with the public key by the mobile apps before sending anonymized data (Figure 28).

Once the professional/practitioner is authenticated, these are projected inside the homepage, with on the left a column as the menu to navigate into the different modules:

- The Homepage: view which shows some information to the users (Figure 31)
- The Agenda: view that shows different in-site/online appointments booked by the users
- The Patient Data: module that shows the different patient's data divided by the health and wellness services provided by the authenticated practitioner/profession (Figure 32). The user's sensitive data are decrypted with the private key to allow the de-anonymization process and the visualization of patient's data to the practitioners/professionals. Moreover, this view shows the users ordered by the priority or alerts scores, calculated by the Data Analytics module depending on the algorithm's rules (Figure 33).
- The Statistics: module which opens a window on the panoramic of statistical data on the app user population
- The Administration: module through which the professional/practitioner can create contents, insert questionnaires, profile modules, etc…

The web app was developed to secure the read and write of data depending on the user's role. The Admin role is the only one that can see all modules and insert all types of data in Administration.

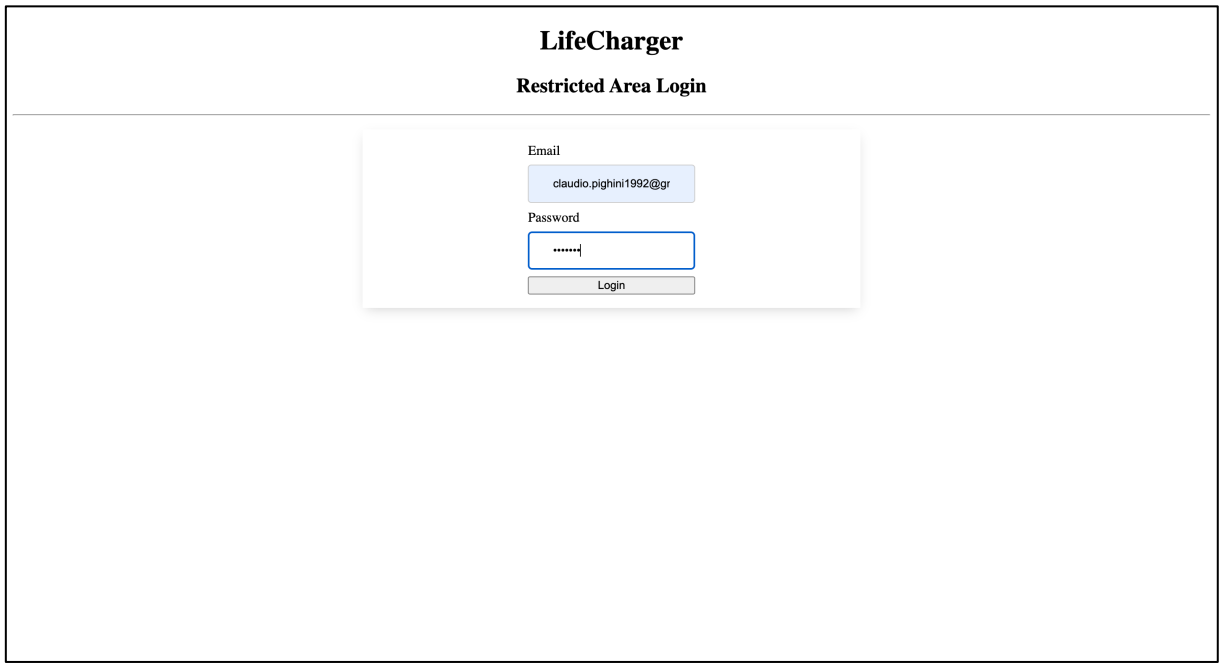

Figure 29: dashboard authentication process with username and password

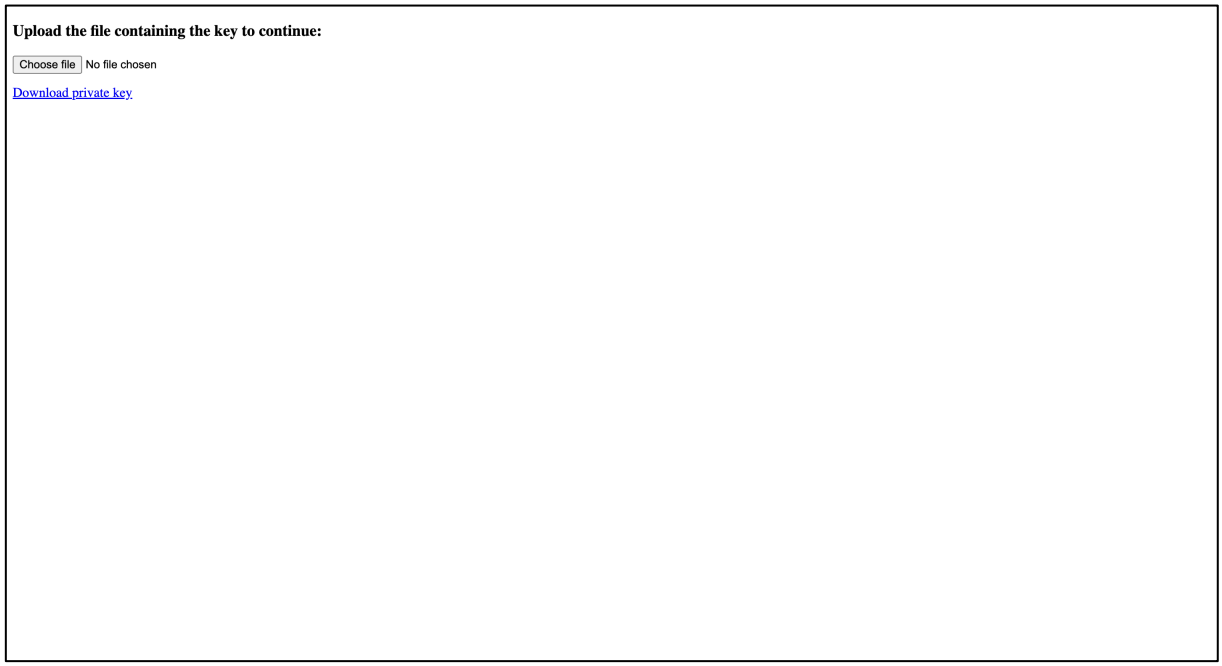

Figure 30: private key insertion to decrypt user's sensitive data for de-anonymization process, after username and password insertion

Figure 31: dashboard homepage and menu (column on the left)

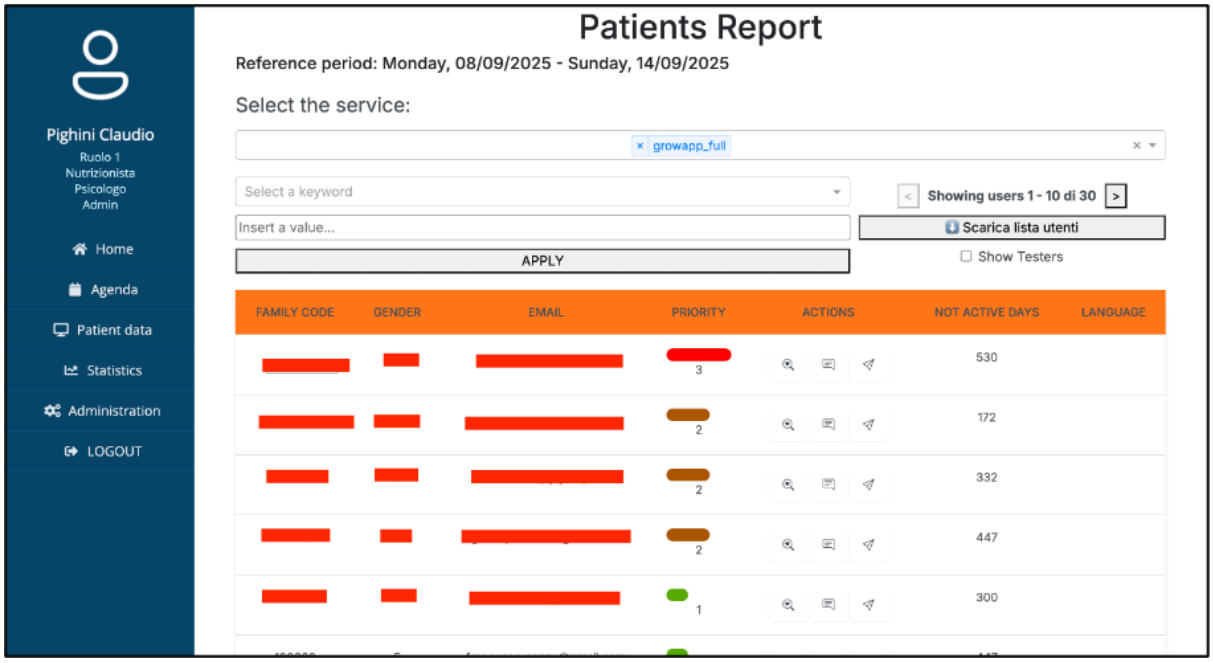

Figure 32: Patient Data module page, where the practitioner/professional selects the service for which operates (growapp-full in this case), and the patient's list is shown, with de-anonymized data

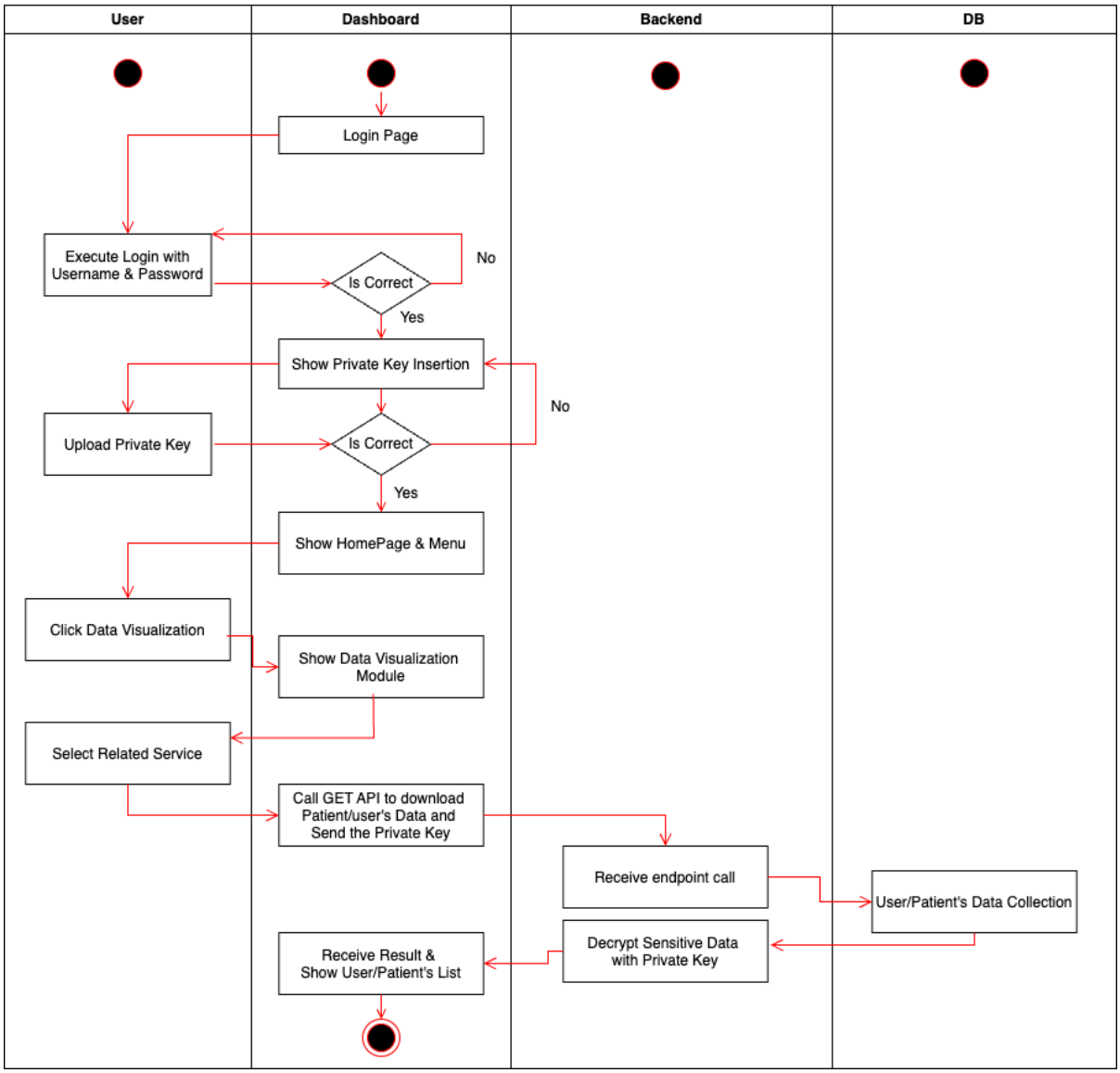

Figure 33: from login to Data Visualization in dashboard (Activity Diagram)

Anyway, the digital informed consents remain the only method to allow the app, thus, the users, sharing data, for both encrypted and pseudo-anonymized.

2.4.2. The Data Analytics Module

As described in the preceding chapter, the pseudo-anonymized data are transmitted from the applications to the repositories in MongoDB Cloud to be subsequently processed by the Data Analytics module, which operates exclusively on data furnished with the users' consent.

The Data Analytics module consists of a series of Python scripts triggered by various routines executed on LifeCharger's local server. These routines invoke Python scripts that:

1. Retrieve the data from the Cloud database;
2. Process the data according to the different objectives and services offered by the platform; and
3. Write back the analyzed results—still in pseudo-anonymized form—to the same Cloud database.

In this way, both the clinician—via the Dashboard—and the user themselves may later retrieve these results for display. Notably, only the application that generated the pseudo-anonymization code and the clinician—by uploading the corresponding private key into the Dashboard environment—are capable of de-anonymizing the data.

2.4.2.1. The Data Processing

The Data Analytics Module data processing is based upon the so called "Routines". The routines are Python scripts that are launched by programmed jobs that the LifeCharger server launches at the established time (Figure 34).

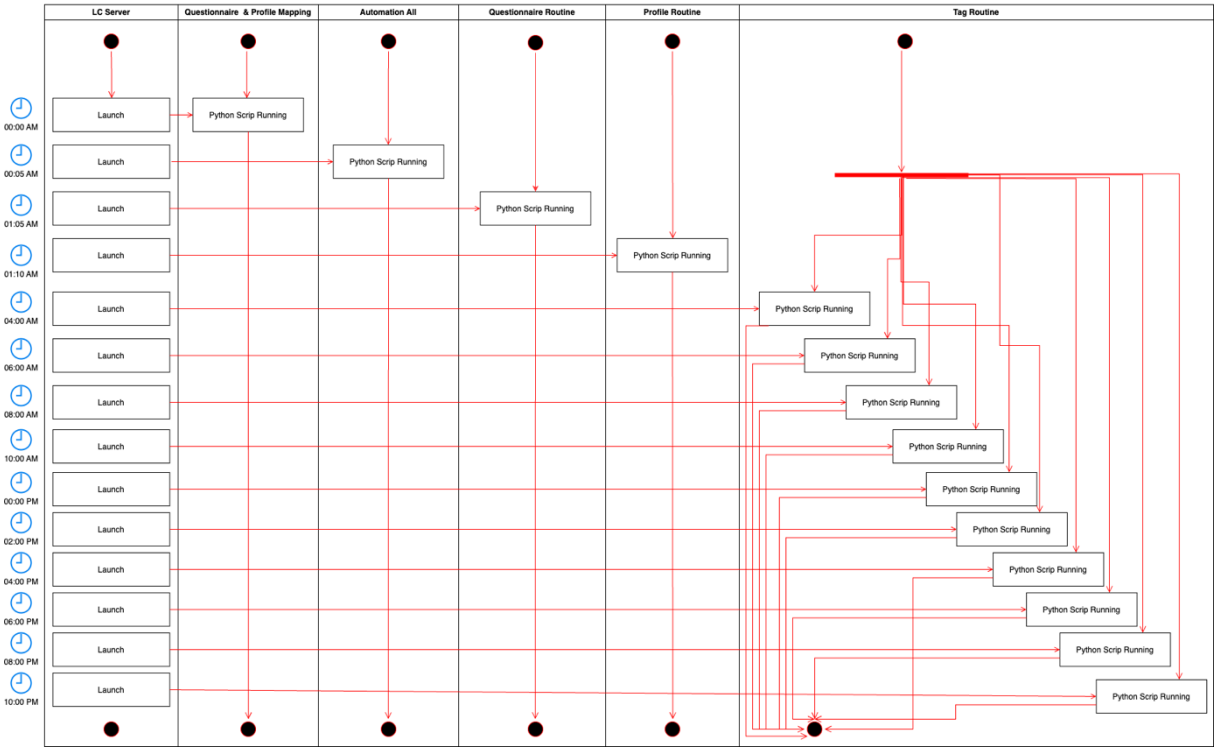

Figure 34: LifeCharger server routine launch (Activity Diagram)

LifeCharger Server

The SynCare Ecosystem utilizes an Apple Mac Mini (Apple M2, 16 GB RAM, macOS v15.4.1) as a dedicated server platform. The compact yet powerful hardware configuration ensures both energy efficiency and high computational throughput, while the latest macOS kernel provides robust process isolation and native support for scripting environments. At the core of Data Analytics module workflow are system agents—configured via macOS's built-in launchd daemon—which orchestrate a series of background routines at predetermined intervals. Each agent is defined by a property list that specifies execution times, environment variables, and logging directives; upon invocation, these agents spawn Python scripts that perform complex data-processing tasks, including data ingestion, transformation, and statistical analysis. By leveraging the Mac Mini's unified memory architecture and M2 neural engine, the server achieves low-latency script execution and accelerated machine-learning inference without dedicated GPU hardware. This architecture demonstrates a reliable, cost-effective solution for continuous, scheduled data workflows in small-scale research and development environments.

"Automation All" Routine

The "Automation All" routine, even if it is launched after the "Questionnaire & Profile Mapping" (Figure 34), represents the main routine. Indeed, the Python script of this routine runs as first Python function the so called "DownloadDeleteDataPool", that downloads all user's data collected by the users the day before of launch, deletes them from database to free space from Cloud DB, and saves them on the local Server. Thus, this first step ensures the alignment of local data to the last collected user's data, on which the Data Analytics module will work on.

After, the "NewCleaningMethod" and "CleanCsv" functions are sequentially run on the same routine script. These Python functions aggregate data on the local tables representing the different data types, and clean them to avoid duplicates.

Following, the script works to update the different report tables:

- the "AppointmentsReports", representing the table of data concerning the booked appoitnments by the users. This contains the different information about each booked appointment (the date, the professional that creates the slot, the related service, etc…);
- the "AdherenceReports", that includes the info about the different calculated therapeutic adherences (drugs, physical activities, questionnaires, and physiological parameters) to the care plan;
- The "DrugsReport", that contains the data about the drugs programmed and taken by the users;
- The "SymptomsReport", representing the table of reported symptoms by the users

- The "ParametersReport", that includes data regarding the different programmed and measured physiological parameters (pressure, abdominal circumference, weight, etc…)

Once updated the cited tables, the scrypt program updates on cloud the computed data for each user through the "UpdateMongoDBCollections" function. After, the scrypt runs the last python functions that are responsible to update the user's registered list. In particular, the "GeneratePatientListWithRelatedServices" and "GeneratePatientListNoServices" update the table verifying which users are already registered and which are new in the system. Moreover, these functions control if service-related informed consents were signed by the users. If a user has signed a consent to activate a service (e.g. psychological consultation), these functions add this info enriching the user's data. This updated user list is visualized by the professionals on the clinical dashboard. Thus, if a professional is allocated to a specific service (e.g. a psychologist to the psychological consultation service), he/she will see the users that have activated the service on the clinical dashboard list (Figure 35)

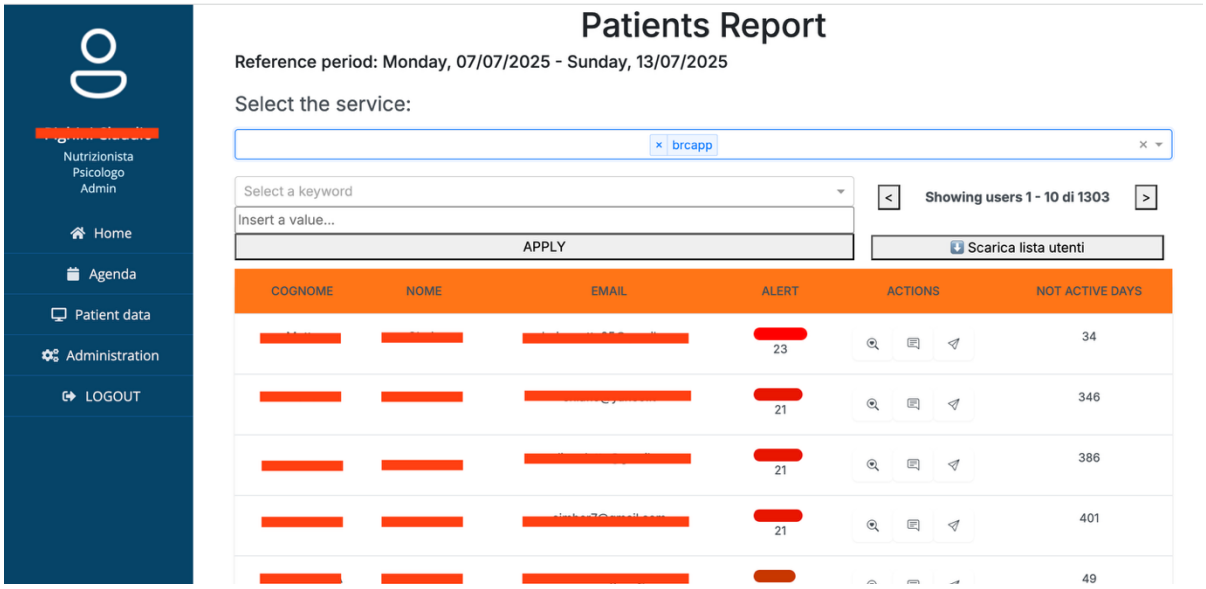

Figure 35: clinical dashboard shows user list to professional. The list is composed as a table with different columns representing user's info fields (surname, name, email, alert, and not active days), in addition to actions presented as three buttons (open panoramic, open messages, and open send care plan module)

In the case of Figure 35, the professional was associated to "brcapp" service, thus, the list of the users was composed of users that have signed a digital consent for "brcapp" service. The sensitive data in Figure 35 are censored, because the authenticated professional can decrypt the sensitive part of the pseudo-anonymized data.

The last part of “AutomationAll” routine is dedicated to compute, through algorithms of the function “GeneratePriorityRecords”, the “Alert” value shown as field of the user’s list on the clinical dashboard (Figure 35). This alert value is the sum of different sub alerts, that are calculated following predetermined rules. These sub-alerts, shown inside the “Alert Details” pop-up window on Figure 36 are associated to a certain alert value (integer value), and their sum represent the total alert shown in the “Alert” column on the user’s list (Figure 35).

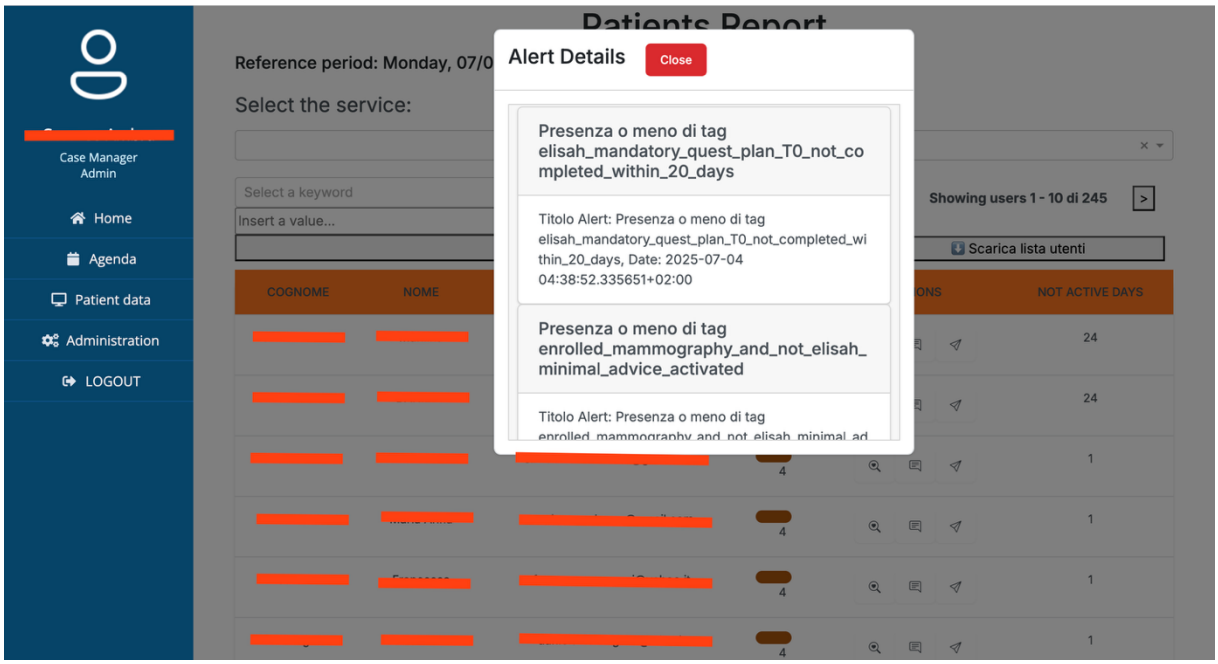

Figure 36: clinical dashboard showing alert details. These alerts were calculated by "GeneratePriorityRecords" Python function of the "AutomationAll" routine. Each sub-alert identifies an alert value, which sum composed the total alert number visualized on the user’s list

Finally, the “UploadAlertReports” Python function of the routine performs the upload of these alert results as reports for each user on the Cloud DB in pseudo-anonymized form.

Figure 37 shows the activity diagram that resumes the “AutomationAll” cited phases.

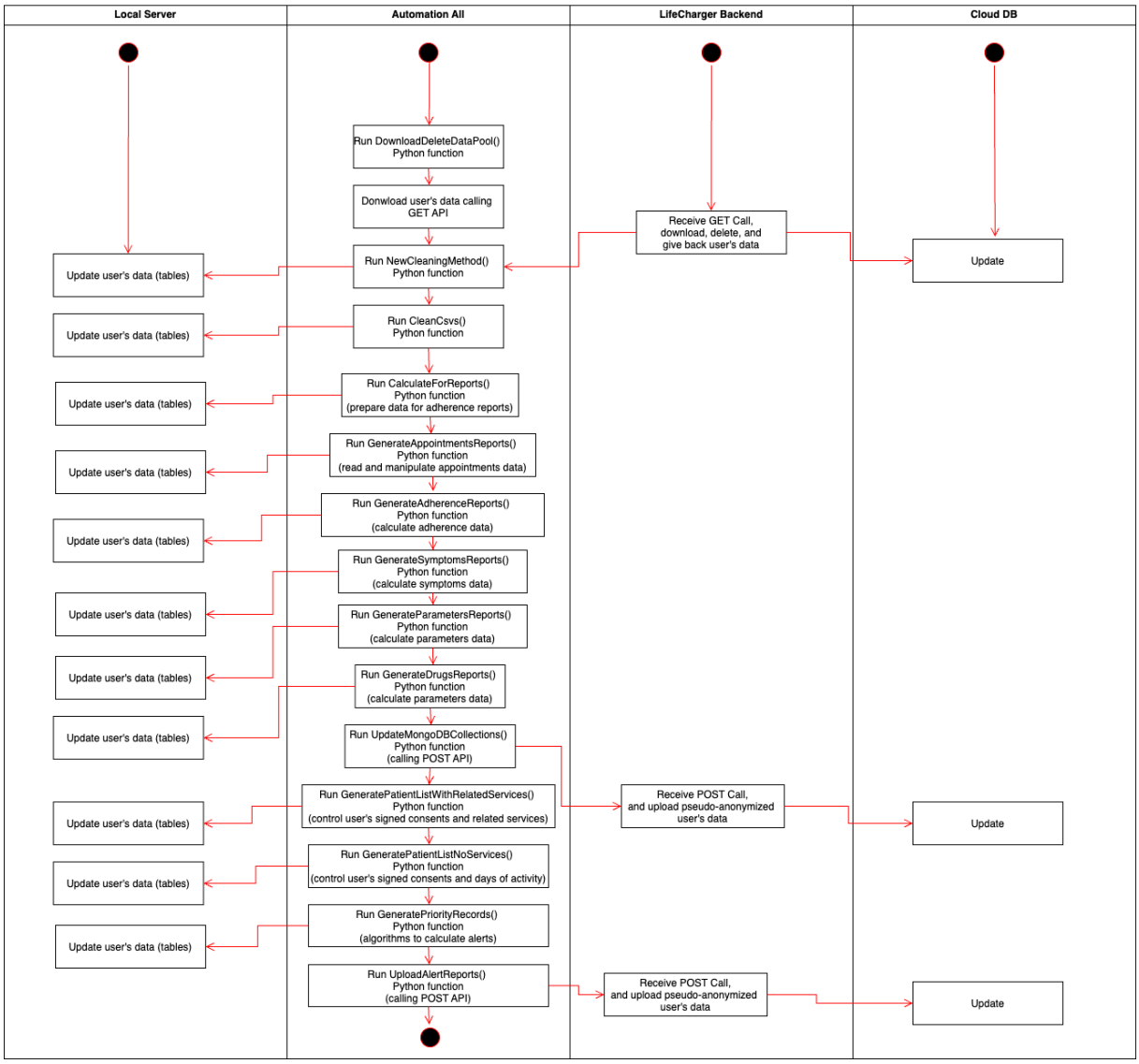

Figure 37: routine "AutomationAll" Python function sequence (Activity Diagram)

Questionnaire & Profile Mapping Routine

This routine called “QuestionnaireProfileMapping” is composed of a series of Python functions with the purpose of generating records that map each questionnaire and profile modules across the various supported languages, according to the schema defined in collaboration with the development team, thereby addressing any multilingual-related issues. Additionally, the function must establish a language-agnostic mapping for each questionnaire and profile module component. This requirement arises from the current database design, in which the distinct elements of a questionnaire or a profile module—the root structure, the questions, and the responses—are each associated with a template_id that encodes language information.

Consequently, the same questionnaire rendered in two languages will possess two different template_id values; similarly, an individual question or response will acquire distinct template_id values when presented in different languages. This allows the clinical dashboard to render the user's questionnaire or profile questions and answers, filled in with using a certain user's smartphone system language, in the browser language.

The Figure 38 resumes the workflow of the "QuestionnaireProfileMapping" routine script.

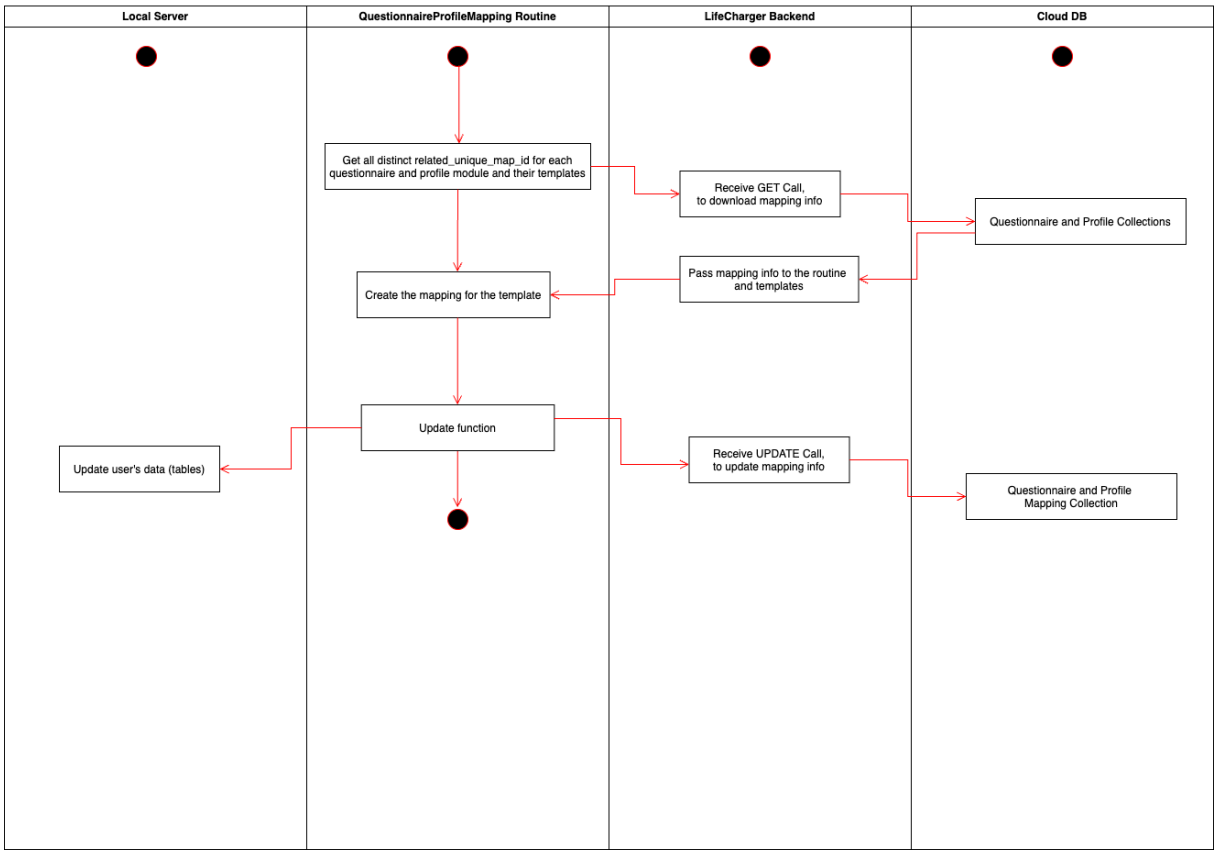

Figure 38: automized "QuestionnaireProfileMappingRoutine" Python function sequence (Activity Diagram)

Questionnaire Routine

The automated "QuestionnaireRoutine" runs in series to the "AutomationAll" routine, which is responsible for updating users' questionnaire tables. It was developed to:

- Automate the updating of the historical questionnaire tables
- Clean up the updated of the historical questionnaire tables
- Populate columns containing mapping information
- Compute scores according to the specific questionnaire algorithms

- Generate individualized reports for each user's completed questionnaires
- Update the locally stored reports on the server and the corresponding collections in the database

The overall data-analysis workflow comprises several stages: extracting up-to-date data from the database; performing data-quality checks and cleansing; and preparing and reloading the processed data so that it can be accessed—via various APIs—by the mobile applications (for end users) and the web dashboards (for professionals and administrators).

Below are the ordered implementation phases of the routine:

1. Append new records to the profiles and questionnaires tables with the appropriate mapping
2. Data cleaning and deduplication
3. Insert mapping info into the questionnaire table
4. Generation of questionnaire reports
5. Calculation of questionnaire scores
6. Insert score into report tables
7. Updating the reports in the database collections

Figure 39 resumes the workflow of the "QuestionnaireRoutine" script.

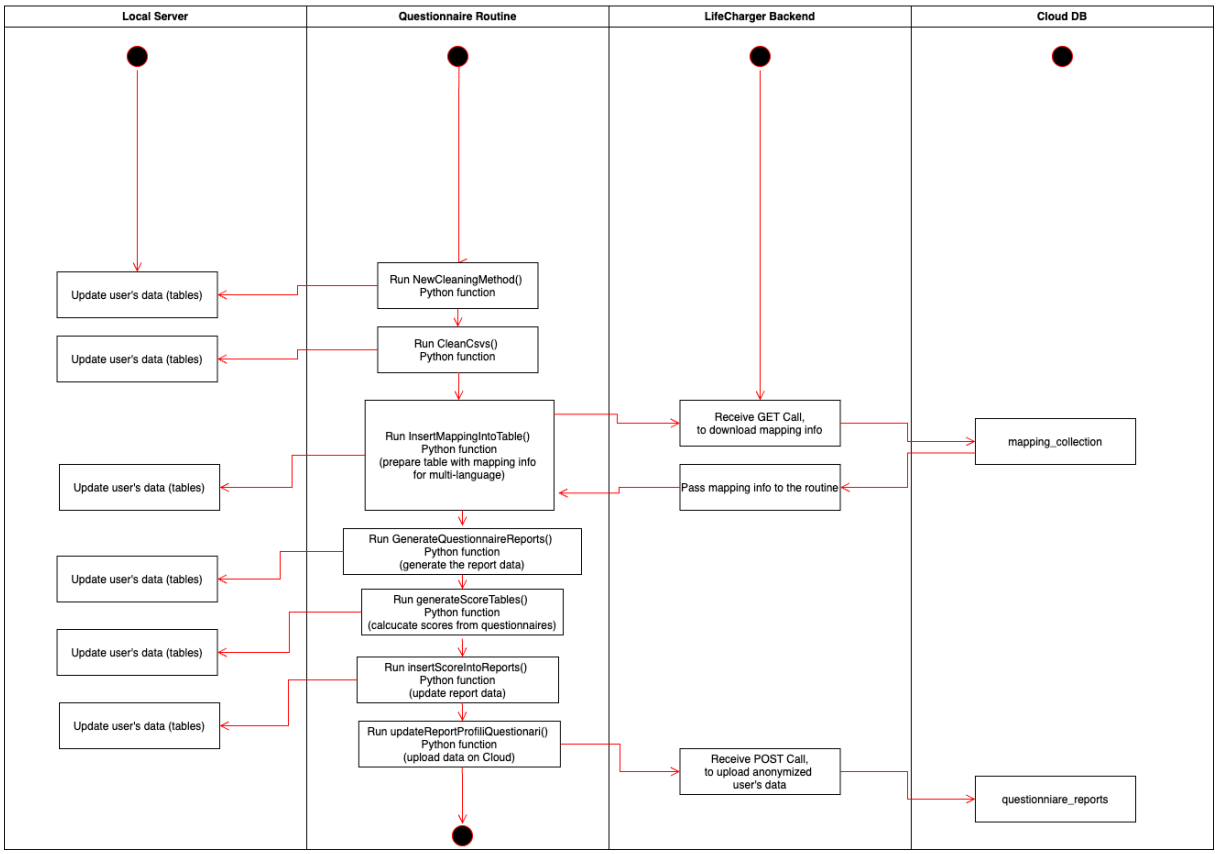

Figure 39: automized "QuestionnaireRoutine" Python function sequence (Activity Diagram)

Profile Routine

Similarly to the "QuestionnaireRoutine", the "ProfileRoutine" runs in series to the "AutomationAll" routine as well, which is responsible for updating users' profile tables. It was developed to:

- Automate the updating of the historical profile tables
- Clean up the updated of the historical profile tables
- Populate columns containing mapping information
- Generate individualized reports for each user's profiles
- Update the locally stored reports on the server and the corresponding collections in the database

The overall data-analysis workflow comprises several stages: extracting up-to-date data from the database; performing data-quality checks and cleansing; and preparing and reloading the processed data so that it can be accessed—via various APIs—by the mobile applications (for end users) and the web dashboards (for professionals and administrators).

Below are the implementation phases of the routine:

1. Append new records to the profiles and questionnaires tables with the appropriate mapping
2. Data cleaning and deduplication
3. Insertion of mapping info into the profile table
4. Generation of profile reports
5. Updating the reports in the database collections

Figure 40 resumes the workflow of the "ProfileRoutine" script.

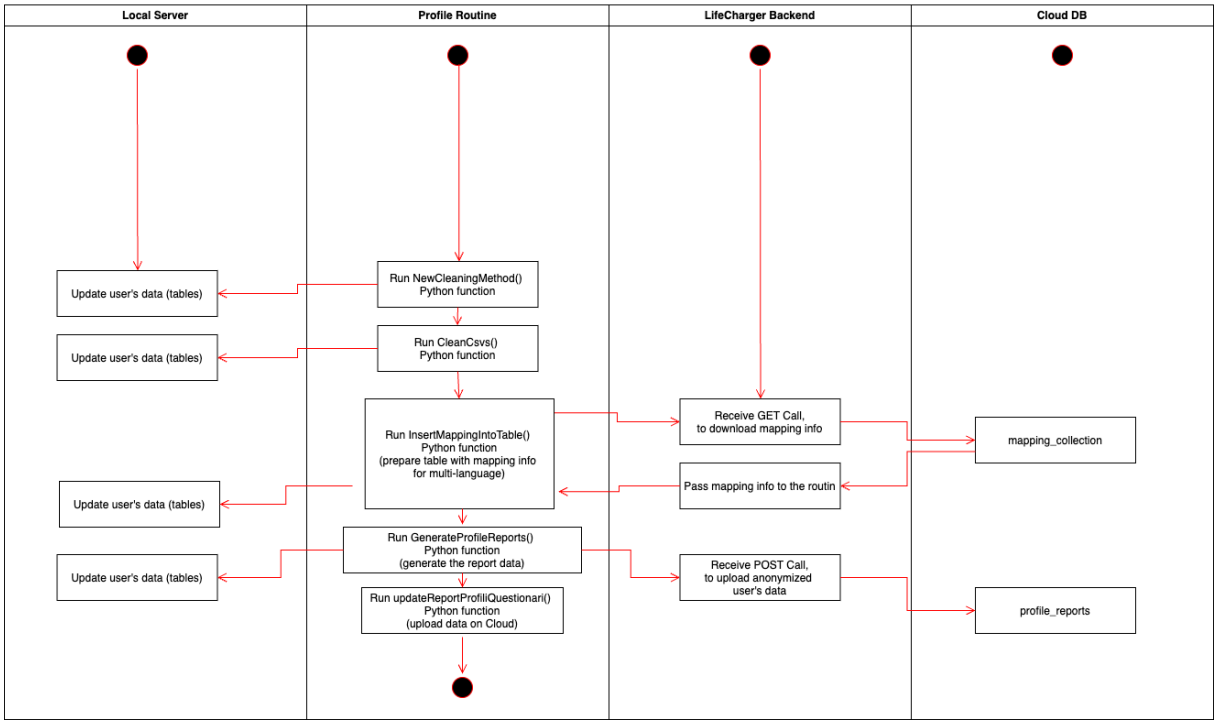

Figure 40: automized "ProfileRoutine" Python function sequence (Activity Diagram)

Tag Routine

The automatic "TagGeneration" routine was developed to streamline the creation of "tags" based on data gathered from users, persisting them directly to the Cloud DB. Subsequently, the records stored in the database collections will be archived locally in a historical table, thereby reflecting the evolution of user tags over time.

The routine comprises the following sequential implementation phases:

1. Retrieval of the "tags" collection from the "GlobalData" database—this lists the various tags along with their descriptions—via API. The Record schema within the "tags" collection is represented by the Figure 41.

Figure 41: record of "tags" that contains the rule information to generate through the routine algorithm the effective user's tag (e.g. if the user has answered to the second answer "2" of the first question "0" of the "profile_map_00030" profile module, the user will be tagged as "smoker")

Every single tag record contains the rule information, written as "rule_description" property, used to generate through the routine algorithm the effective user's tag (e.g. if the user has answered to the second answer "2" of the first question "0" of the "profile_map_00030" profile module, the user will be tagged as "smoker"). The property "trigger_source_type" describes from which collection will be analyzed for extracting the tag, that is strictly related to the "trigger_source_id" (e.g. if the "trigger_source_type" indicates the "profile_report", consequently the "trigger_source"id" will be a profile question or answer info), that contains this info, followed by the "db_name", representing the effective tag name. "is_ans_checked" field was added for a technical reason.

2. The Retrieval—via API—of the already associated tags to the users, from the MongoDB "user_tag" collection, representing the past created tags. The retrieval of these past created tags is necessary because some tag rules (see Phase 1) depend on the previously created tag. For example, a tag could be created because another tag was created 40 days ago (for a reason described by the rule description as in Figure 41), calculated from the "created_at" property (Figure 42).

Figure 42: resulting user's tag record after the "TagGeneration" routine computation in the saved-on Cloud DB. These records represent the associated tags to the users (in an anonymized form represented by an anonymous "user_id"). The "created_at" property represents the date of tag creation.

3. For each entry in the list from "tags" collection (obtained in Phase 1), the routine's script evaluates the user's questionnaire and profile reports in accordance with the tag's "trigger_sousce_type" (Figure 41). Whenever a user's response satisfies a tagging rule (e.g., responding "Yes" to "Are you a smoker?" → assign the "smoker" tag), generate the appropriate tag.

4. Upload of each generated tag—annotated with its attributes ("tag_id", anonymized "user_id", "created_at", and "read" properties)—into the "user_tags" collection within the "GlobalData" database.

Notably in Figure 42, the "read_for_service" and "read_for_plan" attributes are initialized to "false", indicating that the tag has not yet been viewed within the user's application interface. Upon user access, if it is necessary, this flag is set to "true".

The "read_for_plan" property is used to allow the user's app to generate a certain care plan related to the tag (e.g. a user that had a tag "smoker" could have a care plan adapted for quitting smoking). Indeed, when the user's app reads the tag—via API—and generates the care plan, the attribute "read_for_plan" will be set to "true". In the same way, the "read_for_service" property is used to allow the app to activate a certain service related to the user's tag (e.g. the "smoker" user might activate a service, thus, a program, for quitting smoking).

Figure 43 resumes the cited sequence of functions in an Activity Diagram.

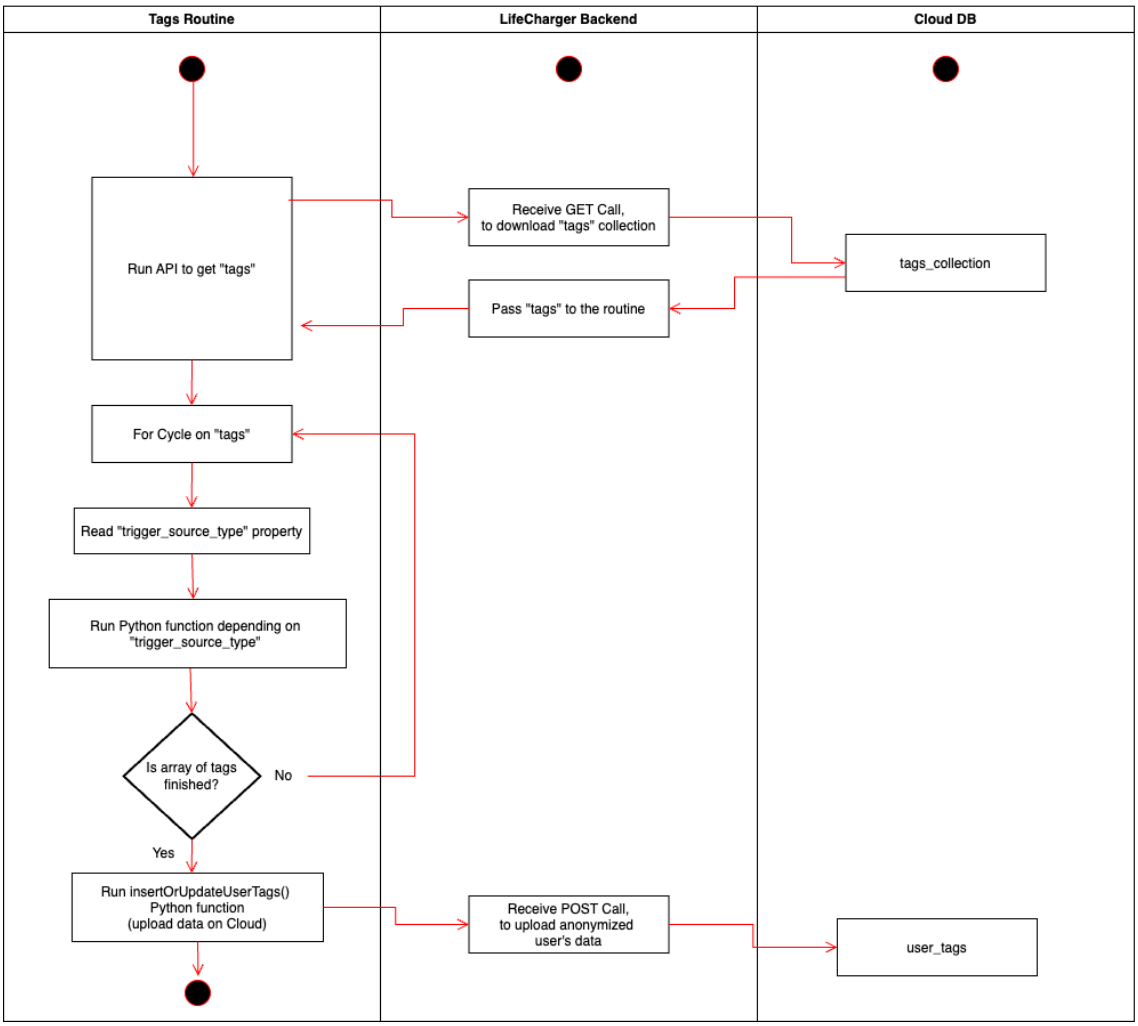

Figure 43: automized "TagsRoutine" Python function sequence (Activity Diagram)

3 LifeCharger Mobile App Usability Evaluation: the e-Brave Study

This chapter describes the usability and acceptability validation of the designed and developed platform described in the previous chapter.

It is a real-word case usability study where the end-users were intended to use autonomously the mobile app, at the basis of the developed RWD ecosystems, in their real-world environments, thus obtaining a usability evaluation and validation in real-world scenarios.

Section 3.1 introduces the real-world case study in which the app usability was evaluated; Section 3.2 explains the materials and methods used to evaluate the app usability and validate the results; Section 3.3 presents the obtained results; e Section 3.4 presents some considerations on the usability evaluation.

Part of the content of this chapter is presented in the following publications:

- ***Claudio Pighini**, Ambra Cesareo, Andrea Migliavacca, and Enrico Gianluca Caiani. 2025. LifeCharger SynCare Mobile App: A Preliminary Usability Study. In Intelligent Human Computer Interaction: 16th International Conference, IHCI 2024, Twente, The Netherlands, November 13–16, 2024, Revised Selected Papers, Part I . Springer-Verlag, Berlin, Heidelberg, 18–28. https://doi.org/10.1007/978-3-031-88705-5_2 [77]*
- *Andreina Oliverio, Carlotta Meli, Eleonora Bruno, Michela Bianchi, Giada Sassi, Elisabetta Venturelli, Ambra Cesareo, **Claudio Pighini**, Margherita Patruno, Maria Di Gennaro, Stefania Tommasi, Antonella Daniele, Silvia Schiavone, Letizia Galasso, Stefano Magno, Gianluca Franceschini, Alberta Ferrari, Robert Fruscio, Daniele Morelli, Claudia Chiodoni , Siranoush Manoukian, and Patrizia Pasanisi. The e-BRAVE study: A prospective web-based cohort and biobank of women carriers of BRCA mutations. Tumori Journal. 2025;0(0). doi:10.1177/03008916251353420 [78]*

3.1. The context

As underlined in the first chapter 1, for mHealth apps to be utilized over time, as this technology is patient-oriented and smartphone-based, it is important to understand the level of perceived quality they offer to the end-users, with a specific focus on evaluating its quality in terms of usability and acceptability [79].

In recent years, besides the typical methods available to evaluate usability and acceptability of a mobile app, such as the System Usability Scale (SUS) and Post-Study System Usability Questionnaire (PSSUQ) [80], a more specific questionnaire has gained relevance: the user version of the Mobile Application Rating Scale (uMARS) [6]. It assesses dimensions of engagement, functionality, aesthetics, information, and subjective quality by a 5-point scale, and it has been largely used to evaluate different mHealth apps, making possible comparisons in literature between different usability studies and results.

In [80], a group of 118 anesthesiologists evaluated an applet-based National Remote Emergency System for Malignant Hyperthermia (MH), using a modified version of uMARS, to deal with MH crises. The evaluation was done after completing some tasks in a simulative utilization. The uMARS was then compared with the results obtained also by the PSSUQ and SUS questionnaires, demonstrating high reliability and validity. In [81], a pilot study was conducted to evaluate usability and acceptability of the FeverDx mobile app with a modified version of uMARS, that was administered to 20 general practitioners to evaluate a simulated emergency consultation of cases of acute febrile syndromes such as Zika, dengue, chikungunya, and other common infections in tropical areas (leptospirosis). In [82], the PREVENTION e-platform, that provides accessible and evidence-based health information tailored to different Breast Cancer (BC) risk levels, was evaluated via uMARS by 30 women. This was done by assigning randomly the 30 women to a BC risk level, and they could access only the info of the assigned section. In [83], 126 rheumatic patients evaluated Rheuma Auszeit self-management mobile app with a simplified version of uMARS after at least 10 minutes using a tablet. Finally, in [84], 26 patients assessed Convoy-Pal, that is a mobile intervention to deliver self-management tools and palliative care to older adults with advanced heart failure. The patients evaluated the usability of the Convoy-Pal after an interview between 40 and 60 minutes, where tools and characteristics of the system were shown.

The Table 1 summarizes the cited related works emphasising the initial interaction with the users and real-world short-term engagement for usability evaluation.

Table 1: summary of related works that highlights initial user interaction and real word short-term engagement for usability evaluation

Reference	App/System	Participants	Method (uMARS / other)	Context of Evaluation	Key Notes
Yu, H., et al., A WeChat applet-based national remote emergency system for malignant hyperthermia in China: a usability study. [80]	National Remote Emergency System for Malignant Hyperthermia (MH)	118 anaesthesiologists	Modified uMARS + SUS + PSSUQ	Simulation of MH crisis tasks	High reliability/validity across tools; focus on simulation, not first-use experience
Rodríguez, S., et al., Acceptability and usability of a mobile application for management and surveillance of vector-borne diseases in Colombia: An implementation study. [81]	FeverDx (acute febrile syndromes: Zika, dengue, etc.)	20 general practitioners	Modified uMARS	uMARS Simulated emergency consultations	Small pilot; evaluation in controlled scenario, not real clinical workflow
Attieh, S., et al. Perceptions and Usability of PREVENTION: A Breast Cancer Risk Assessment e-Platform. [82]	PREVENTION e-platform (BC risk info)	30 women (randomly assigned BC risk level)	uMARS	Access to tailored info sections	Controlled exposure; no observation of repeated or real-world use
Lambrecht, A., et al., Quality of a Supporting Mobile App for Rheumatic Patients: Patient-Based Assessment Using the User Version of the Mobile Application Scale (uMARS). [83]	Rheuma Auszeit (self-management for rheumatic patients)	126 patients	Simplified uMARS	≥10 min tablet use	Short interaction; no longitudinal or contextual data
Villalobos, J.P., S.S. Bull, and J.D. Portz, Usability and Acceptability of a Palliative Care Mobile Intervention for Older Adults With Heart Failure and Caregivers: Observational Study. [84]	Convoy-Pal (self-management & palliative care for heart failure)	26 older adults with advanced HF	uMARS (interview-based)	40–60 min guided interview	One-time exposure; usability judged after demo, not real-world adoption

As briefly described, mHealth usability studies often do not consider initial user interaction, or the impact of real-world settings on short-term engagement. Moreover, the basic functions of the applications (such as, self-reporting, filling questionnaires, etc...) are not evaluated separately from those used within the provided digital health or wellness service.

This usability study has the purpose to evaluate via uMARS questionnaire the perceived usability and acceptability of the mobile app called BRCApp, developed by LifeCharger (LC), used by the volunteers taking part of e-Brave study in their real-world environment.

The e-Brave study aims to create an Italian web-cohort and biological bank of at least 1000 women carriers of Breast Cancer (BRCA) 1/2 pathogenic variants and unaffected by any BRCA-related cancer, to investigate over time the role of potential penetrance modulators in the occurrence of primary BRCA-related cancers. In detail, the associations between genetic (polymorphisms), environmental modulators (lifestyle/metabolic/hormonal/anthropometric/inflammatory factors) and health outcomes (incidence of BC/OC/other BRCA-related cancers) will be tested. Then, potential mechanisms by which the environmental modulators under study affect BRCA penetrance will be also explored. Specifically, lipidomics (main focus on ceramides, di-triglycerides, phosphatidilcholines, lysophosphatidilcholines and plasmalogens), metabolomics, epigenetics (key miRNAs) and markers of microbiota (plasma SCFA) and dysbiosis (Lipopolysaccharide) will be investigated.

The e-BRAVE study is expected to last five years including recruitment/creation of the web-cohort (in the first three years) and survival and mechanistic analyses (in the last two years). However, the e-BRAVE web-based cohort represents the starting point of a potentially larger "open" digital platform to be followed-up for a longer period and to be implemented with additional BRCA people, and new data and analyses.

The Web-Cohort is represented by the study volunteers, aged 18-70 years, with no clinical evidence of cancer, that have access to internet through their smartphones and use a dedicated mobile app (BRCApp). The recruitment of women carriers of BRCA1/2 mutations will be carried out for the first three years of the study.

3.2. Materials and Methods

The e-BRAVE study was approved by the Istituto Nazionale Tumori (INT) ethics committee Act N° 30/24, and the recruitment, through the mobile BRCApp registration, started on June 28th, 2024, and it is currently undergoing, letting the volunteers download the app from Apple and Google Play Stores and begin the e-Brave study in every moment.

3.2.1. The BRCApp and its Ecosystem

The BRCApp is a mobile app that represents the main end-user front-end, as part of the developed innovative digital ecosystem (LifeCharger SynCare, Chapter 2) designed to gather cohort information, enhancing synergy between project participants and researchers. The BRCApp platform aims to support women's engagement, adherence to treatment, intervention plans, and self-empowerment, complemented by activity tracking and monitoring. Thus, the BRCApp through its Ecosystem becomes able to create clusters of users, applying the related journey including activities to be performed in app (physiologic and body parameters to be measured, questionnaires to be filled in and informative contents to read).

3.2.1.1. The BRCApp

Upon subscribing to the BRCApp (using email and password), the users receive a confirmation email. At this point, they gain access to the BRCApp via the login section, using their email and password, and signing the digital informed consent form (mandatory steps, Figure 44).

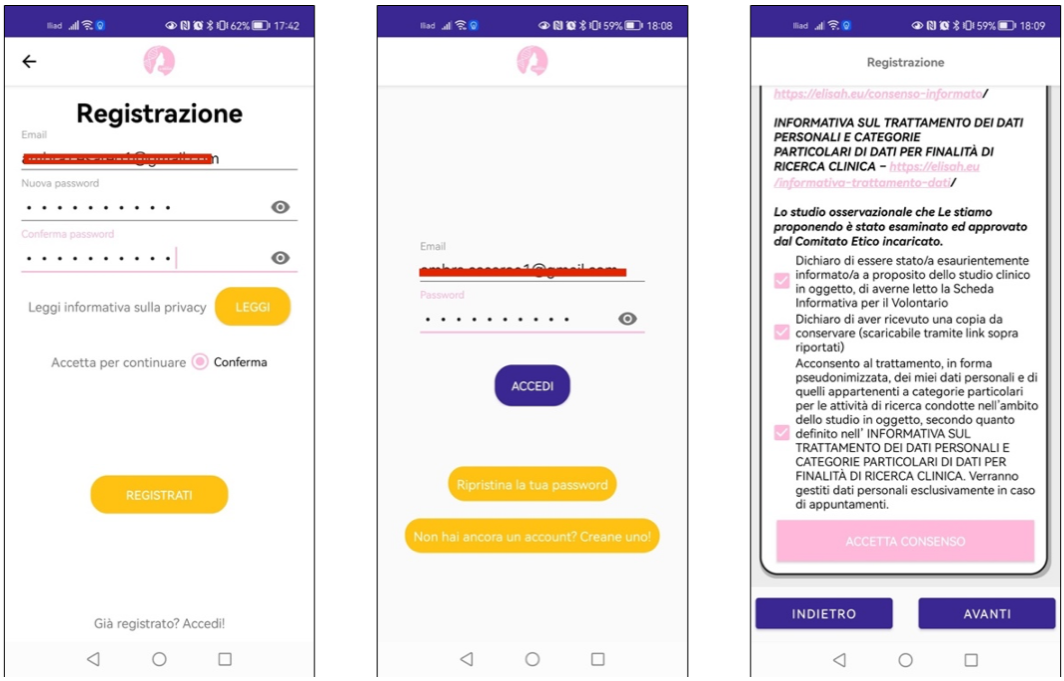

Figure 44: On the left and on the center, the Registration and Login of user account screenshots, respectively; on the right, the mandatory digital informed consent, that is saved on the Ethereum Blockchain

Through the HOME page of the BRCApp (Figure 45), the users have access to different functionalities:

- “PROFILE,” that includes all the modules needed to gain basic information on users at the starting point. This information is useful for associating tags to the users and customizing their journey (i.e, women who declare they have a situation of reduced mobility are offered mild contents relating to physical activity);
- “YOUR DAY” (Figure 46), that lists all the activities scheduled for the day, allowing users to input requested measurements, fill in questionnaires, etc.;
- “APPOINTMENTS”, that allows users to view availability for different types of appointments provided by the activated services, book appointments (including clinical visit and blood examination), to view details about the reserved appointments (date, hour, location, additional information, etc.) and cancel appointments;
- “ADHERENCE & REPORTS”, that provides an overview of user’s path, including adherence to treatment/intervention, trends of physiologic parameters, physical activity, etc.;
- “SYMPTOMS”, that allows to easily report symptoms and add them to their daily diary;
- “DOCUMENTS”, that allows users to upload, manage and organize documents such as clinical reports, prescriptions, care plans, etc., by creating different folders and adding notes;
- “CONTENTS”, that collects all the informative and training materials received by the user, organized into categories for easy access;
- “SERVICES”, that allows users to activate and manage services, such as webinar.

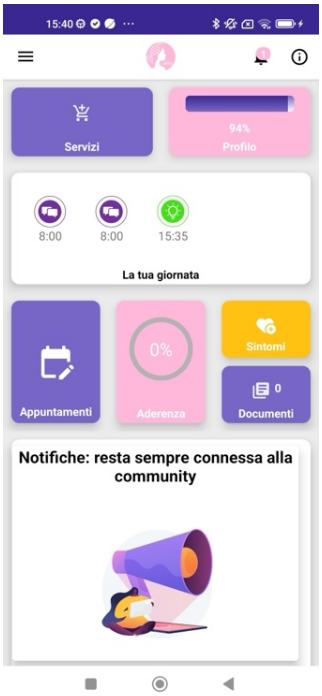

Figure 45: Home screenshot: the user can access different sections through the home shortcut buttons ("Activated Services", "Profile", "Your Day" view, "Appointments", "Adherence" & "Reports", "Documents", "Symptoms", "Suggestion and Contents")

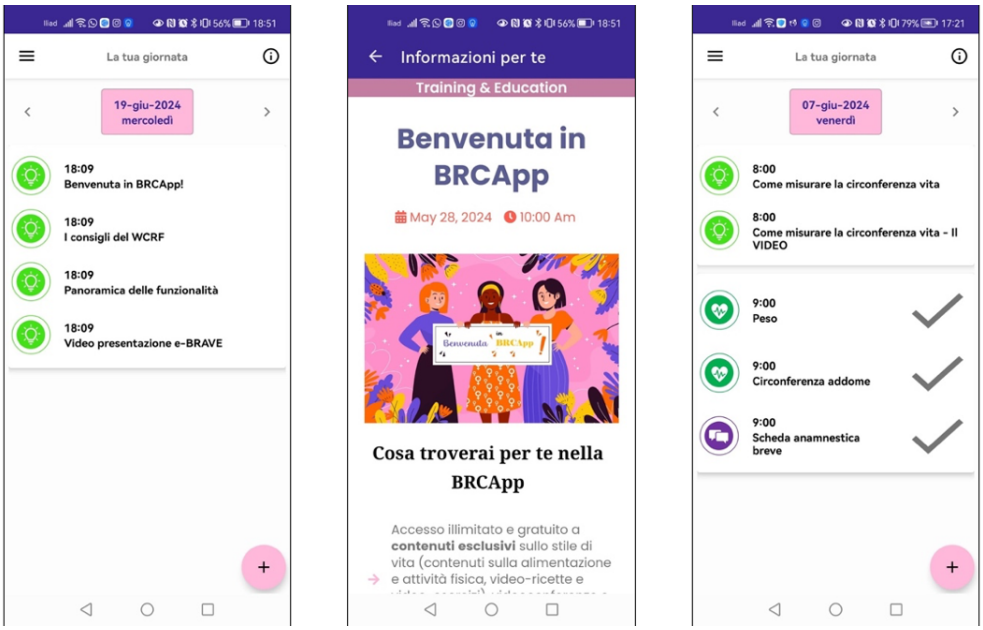

Figure 46: Section "Your Day" presenting day by day the activities to perform (e.g. insert weight and abdominal circumference, and questionnaires) and the contents to read (suggestions, etc…)

Once become a member, the user/patient must complete a short anamnestic form (including height and body weight), through the "Profile" section, the short screener of adherence to Mediterranean diet (er-MEDAS) and the Godin leisure-time questionnaire, through the "Your Day" view (Figure 46), and book the clinical visit and blood examination according to a predefined list of appointments at the nearest collaborating centre, through the "Appointments" section. Participants are required to provide a copy of their genetic test the day of the clinical visit. Reminder emails/in-app notifications are sent to obtain completed forms/blood samples within three months. Further questionnaires are scheduled in the subsequent months following a pre-defined timeline and according to the season:

- The Energy-restricted Mediterranean Diet Adherence Screener (er-MEDAS), a short questionnaire on adherence to Mediterranean diet that captures the dimension of moderation of food consumption and energy restriction. Er-MEDAS consists of 17 items, 14 items on food frequency consumption and 3 on eating habits. Compliance with each of the 17 items is scored with 1 point. Therefore, the total er-MEDAS score ranges from 0 to 17, with 0 indicating no adherence and 17 the maximum adherence.
- The Godin Shepard Leisure-Time Physical Activity Questionnaire (GSL-TPAQ), to assess the amount of leisure time physical activity (PA) performed in the last seven days by including three questions about the frequency of PA (number of activities/week). Each question refers to PA of different intensity (one question on mild, one on moderate and one on strenuous PA) which corresponds to a specific Metabolic Equivalent of Task (MET) amount. Mild PA corresponds to 3 METs, moderate PA to 5 METs and Strenuous PA to 9 METs. The total GSL-TPAQ score is obtained using the following formula: (frequency of mild × 3) + (frequency of moderate × 5) + (frequency of strenuous × 9). If the final score is < 24, the subject is classified as inactive, while in the opposite case (≥ 24) is described as active.
- The International Physical Activity Questionnaire (IPAQ) that identifies the total minutes over the last 7 days spent on moderate PA, vigorous PA, walking, and inactivity. The questionnaire collects information on time (i.e. number of sessions and average time per session) spent walking, participating in moderate-intensity physical activity, participating in vigorous-intensity physical activity and sitting, on weekdays and weekend days. Questions regarding participation in moderate and vigorous physical activity are supplemented by concrete examples of activities commonly performed. Data from the questionnaire are summed within each item (i.e., vigorous-intensity activity, moderate-intensity activity, walking) to estimate the total amount of time spent in physical activity per week. The total IPAQ score is obtained using the following formula: for vigorous PA (minutes * days * 8 MET) + moderate PA (minutes * days * 4 MET) + walking (minutes * days * 3.3 MET). If the final

score is < 700, the level of PA is considered LOW. If the final score is between ≥ 700 and < 2519, the level of PA is considered MODERATE, while if the final score is ≥ 2519 the level of PA is considering HIGH.

- The Reduced Morningness-Eveningness Questionnaire (r-MEQ) that consists of 5 multiple-choice items that investigate the chronotype, where lower scores indicate eveningness and higher scores morningness. Each response is assigned a score between 0 and 6. The total score for the items ranges from 4 to 25. Scores ranging from 4 to 11 indicate evening preference, differentiated in definite E-type (scores 4–7) and moderate E-type (scores 8–11); scores ranging from 18 to 25 indicate morning preference, differentiated in definite M-type (scores 22–25) and moderate M-type (scores 18–21). Scores from 12 to 17 indicate neither accentuated morning or evening preference, and people with scores in this range are categorized as being N-type.
- The Generalized Anxiety Disorder scale (GAD-7) that with seven items describes the most important diagnostic criteria according to DSM-IV-TR (27), namely Criterion A (fear and anxiety related to a series of events or activities), Criterion B (difficulties in controlling concerns) and Criterion C (anxiety and worry are accompanied by at least three additional symptoms such as restlessness, mild fatigue, difficulty concentrating, irritability, muscle tension and sleep problems). The GAD-7 asks how often people have suffered from the seven core symptoms of GAD within the last two weeks with the response options being “not at all,” “early days,” “more than half the days,” and “nearly every day,” scored as 0, 1, 2, and 3, respectively, with a total score ranging from 0 to 21. Scores ranging from 0 to 4 indicate minimal anxiety, from 5 to 9 mild anxiety, from 10 to 14 moderate anxiety, and scores from 15 to 21 indicate severe anxiety.

Table 2: Summary of the different questionnaires administered during the e-Brave study

Questionnaire Name	Brief Description
Energy-restricted Mediterranean Diet Adherence Screener (er-MEDAS)	Short questionnaire on adherence to Mediterranean diet that captures the dimension of moderation of food consumption and energy restriction
Godin Shepard Leisure-Time Physical Activity Questionnaire (GSL-TPAQ)	Assessment of the amount of leisure time physical activity (PA) performed in the last seven days by including three questions about the frequency of PA (number of activities/week)
International Physical Activity Questionnaire (IPAQ)	Identification of the total minutes over the last 7 days spent on moderate PA, vigorous PA, walking, and inactivity
Reduced Morningness-Eveningness Questionnaire (r-MEQ)	5 multiple-choice items that investigate the chronotype, where lower scores indicate eveningness and higher scores morningness
Generalized Anxiety Disorder scale (GAD-7)	Description of the most important diagnostic criteria according to DSM-IV-TR (27), namely Criterion A (fear and anxiety related to a series of events or activities), Criterion B (difficulties in controlling concerns) and Criterion C (anxiety and worry are accompanied by at least three additional symptoms such as restlessness, mild fatigue, difficulty concentrating, irritability, muscle tension and sleep problems)

Through the BRCApp, participants have continuous free access to a wealth of content about lifestyle (recommendations, web kitchen/exercise courses, and recipes), study progress, potential risk/protective factors, regulatory news, and information about patients' associations (Figure 47).

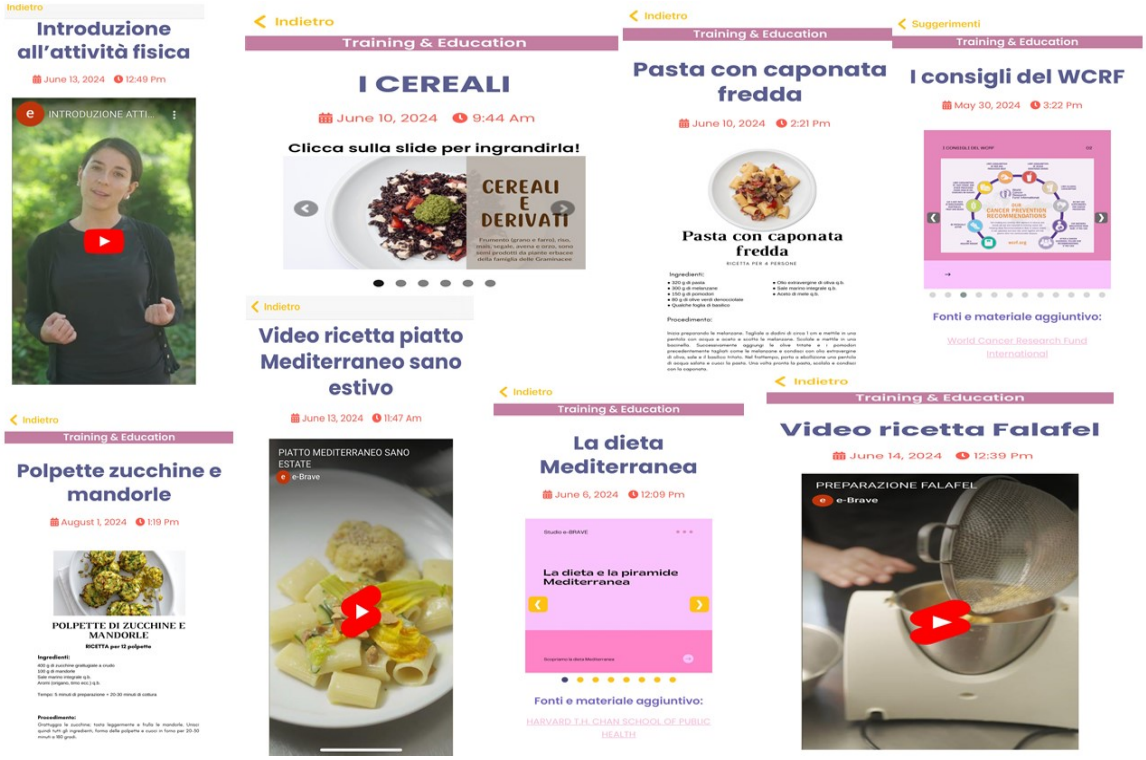

Figure 47: BRCApp lifestyle' contents (recommendations, web kitchen/exercise courses, and recipes)

The BRCApp allows participants to access all the lifestyle contents and activities (textual contents, recommendations, web kitchen/exercise courses, video-recipes/exercises and a calendar for participating to informative webinar) according to a pre-defined timeline. The textual contents are short, easy to read, and initially on general topics ("The Mediterranean diet", "The benefits of physical activity", "The healthy breakfast" etc.); after the first few months, as participants' knowledge increases, the contents become more focused ("Probiotics and fermented food", "The high-processed food" etc).

Dietary contents are based on the Mediterranean dietary principles/recipes. The contents are created to improve women' knowledge about diet as important strategy for prevention, to gain greater awareness about food and nutrients, to help them choosing foods consciously and to control body weight.

PA contents are created to encourage women to reduce sedentary behaviour, and to achieve and maintain regular participation in a moderate intensity physical activity for 210 minutes/week (30 minutes on average per day). PA contents include sessions, with detailed exercise descriptions, and images and videos. The videos include simple and easy-to-perform exercises involving small muscle groups.

3.2.1.2. The In-App Journey and Tag Generation

During the app utilization, the LC BRCApp back-end creates at different timepoints different user's labels called "tag" to keep track of the user situation and drive them into different path of app utilizations.

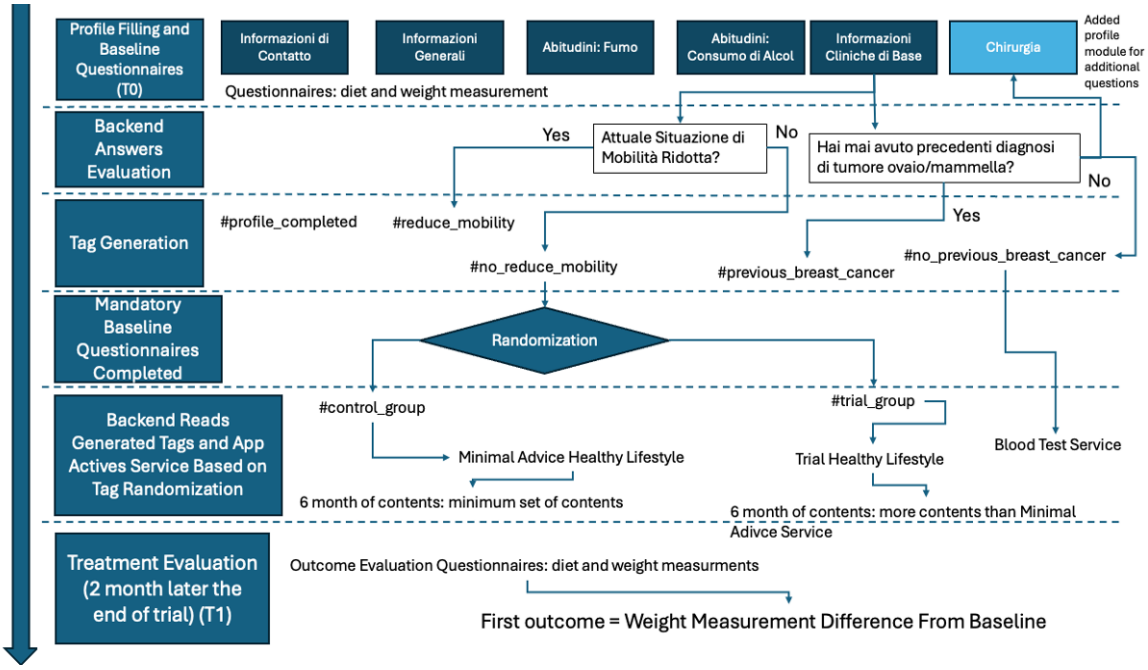

Figure 48: In-App study journey, from "Profile Filling and Baseline Questionnaires" to "Treatment Evaluation"

After the app registration, the e-Brave users start with the In-App journey (Figure 48), that consists in profile and baseline questionnaires completion, flanked by physiological parameters insertions, such as weight and abdominal circumference. When these information are inserted and read by the BRCApp back-end, from the user's answers to the profile (Figure 48, Profile Filling and Baseline Questionnaires) the tags to identify the differentiation among control and trial groups are created (Figure 48, Back-end Answers Evaluation to Tag Generation). Thus, once the users have also filled the baseline questionnaires, the back-end randomly assign to the users with tag #no_reduce_mobility the control and trial group tags (Figure 48, Mandatory Baseline Questionnaires Completed).

These tags are essential to drive the user into different branches of BRCApp use. Indeed, the users into the #trial_group receive suggestions and contents about physical activities, while #control_group users receive a reduced set of contents without physical activity advice, as well as the group that are tagged as #reduced_mobility, being not able to conduct the trial study (Figure 48, Backend Reads Generated Tags and App Actives Service Base on Tag Randomization).

The second essential tag is that regarding the previous diagnosis of breast or ovarian cancer. Indeed, the users that are tagged as #no_previous_breast_ovarian_cancer are asked to book through the app a blood test, in the available centres (Figure 48, Tag Generation).

After the users are tagged by the LC back-end, the different clusters allow the app to create different paths of use, and this is possible through the activation of so called "services". Depending on what tags are created, the LC back-end creates different app services that the BRCApp reads to activate for the users' different contents, suggestions, and advice (Figure 48, Backend Reads Generated Tags and App Actives Service Base on Tag Randomization).

The Table 3 summarises the different services that the user's app should activate, depending on tag combination. In particular, the Minimal Advice Healthy Lifestyle (Healthy) and (Sick) content are equal, as well as for the Trial Healthy Lifestyle (Healthy) and (Sick), but they are labelled differently just to differentiate the "healthy" and "sick" groups.

Once the services are activated, the App shows advice, suggestions, and contents to the users for six months. The Minimal Advice Healthy Lifestyle (Healthy) and (Sick) contains a minimum set of contents, while Trial Healthy Lifestyle (Healthy) and (Sick) shows a set of contents chosen to influence the user's lifestyle behaviour about diets and physical activity.

Table 4 shows the questionnaires and measurements that are provided to the users for the baseline (T0) and for the evaluation (T1) moments (Figure 48, T0 and T1 steps). In particular, the only difference between "Sicks" and "Healthy" users is a questionnaire "Clinica Studio Sperimentale con Farmaco".

Table 3: Tag combinations associated by the LC back-end to users depending on profile answers and the Services that the BRCApp activated allowing the users to received differentiated contents and care plans

Tag Combination	Services
#no_previous_breast_ovarian_cancer	Blood Test
#reduced_mobility + #no_previous_breast_ovarian_cancer	Minimal Advice Healthy Lifestyle (Healthy)
#reduced_mobility + #previous_breast_ovarian_cancer	Minimal Advice Healthy Lifestyle (Sick)
#no_reduced_mobility + #no_previous_breast_ovarian_cancer + #elisah_control_group	Minimal Advice Healthy Lifestyle (Healthy)
#no_reduced_mobility + #no_previous_breast_ovarian_cancer + #elisah_trial_group	Trial Healthy Lifestyle (Healthy)
#no_reduced_mobility + #previous_breast_ovarian_cancer + #elisah_control_group	Minimal Advice Healthy Lifestyle (Sick)
#no_reduced_mobility + #previous_breast_ovarian_cancer + #elisah_trial_group	Trial Healthy Lifestyle (Sick)

Table 4: Baseline (T0) and Evaluation (T1) questionnaires and measurements provided to the users depending on tags

Tag	Care Plan
Healthy (#no_previous_breast_cancer)	Physiological Parameters: - Abdominal Circumference (T0-T1) - Weight (T0-T1) Questionnaires: - Scheda Anamnestica Breve (T0-T1) - Er Medas (T0-T1) - Godin (T0-T1) - MSQ (T0-T1) - Clinica (T0-T1) - IPAQ (T0-T1) - rMEQ (T0-T1) - GAD-7 (T0-T1) - Clinica Studio Sperimentale con Farmaco
Sick (#previous_breast_cancer)	Physiological Parameters: - Abdominal Circumference (T0-T1) - Weight (T0-T1) Questionnaires: - Scheda Anamnestica Breve (T0-T1) - Er Medas (T0-T1) - Godin (T0-T1) - MSQ (T0-T1) - Clinica (T0-T1) - IPAQ (T0-T1) - rMEQ (T0-T1) - GAD-7 (T0-T1)

Table 5 shows the principal functionalities added to the BRCapp depending on which service is activated during the App journey.

Table 5: BRCApp additional functionalities for the users depending on activated services

Activated Service	Additional Functionalities
Blood Test	- Blood Test Booking - Added profile module "Chirurgia"
Minimal Advice Healthy Lifestyle (Healthy/Sick)	Minimum Set of Contents
Trial Healthy Lifestyle (Healthy/Sick)	More Contents with Physical Activity Advice

3.2.2. The Usability Study

After at least 7 days of BRCApp use, the uMARS questionnaires were administered, digitally in-App, to the e-Brave's users, to evaluate the perceived usability.

All pseudo-anonymized data were extracted from the LC Cloud Database (DB) and analyzed using a python script on PyCharm IDE.

To obtain the overall usability uMARS score, the mean of each objective subscale was derived, and their means and medians computed. This score represents the objective quality of the app, while the means and medians of the two sections E and F represent the perceived subjective quality by the users and the future perceived impact of this technology on the users themselves, respectively.

To understand if there is a correlation between the obtained scores of the different uMARS sections and the effective user's days of use, thus, for demonstrating the impact of the app usability on its effective real-world use, the Spearman's Correlation was used.

The user's uMARS scores were grouped into different subgroups, depending on a threshold (TH) that represents the minimum days of use for being considered for the different analysis. The TH was used to consider a user into the subgroup if and only if the user used the app more days than or equal to TH, before and after the uMARS questionnaire filling date. A value of TH=1 means including all the users without considering users which could have stopped to use the app after uMARS compilation, thus, without re-open the app at least once.

The days of use were computed by analyzing the BRCApp Logs. If a user viewed in a day the BRCApp home page, this represented a day of use. The days of use were considered from the user registration date on the BRCApp to the date of data download for the analysis.

For each subgroup the Spearman's correlation was calculated, repeating it for the different section scores: the obtained Overall uMARS score (the mean of the main four sections), for the Section A (Engagement), for the Section B (Functionality), for the Section C (Aesthetics), and for the Section D (Information).

The subgroups were created considering an incremental TH from 1 (all users without users which stopped to use the app after uMARS compilation) to 90 (three months of use). The obtained Spearman's RHO correlation coefficients were considered as significant if the p-values were < 0.05.

The usability evaluation continued by comparing two sub-groups of users from the entire sample, the control and trial groups, which were tagged as #no_reduce_mobility and randomized into the two groups.

To statistically analyze the questionnaire results of these two independent groups, the same Sperman's Correlation technique was used. In this case, the difference relied on the comparison of the Sperman's Correlation results, obtained for each TH subgroups and score sections, between the control and the trial groups. Moreover, the considered TH were only 1, 5, and 7, to avoid low sample sizes for the comparison and considering 5 and 7 days of use as enough to have a reliable usability evaluation.

The Figure 49 summarizes the usability analysis described process.

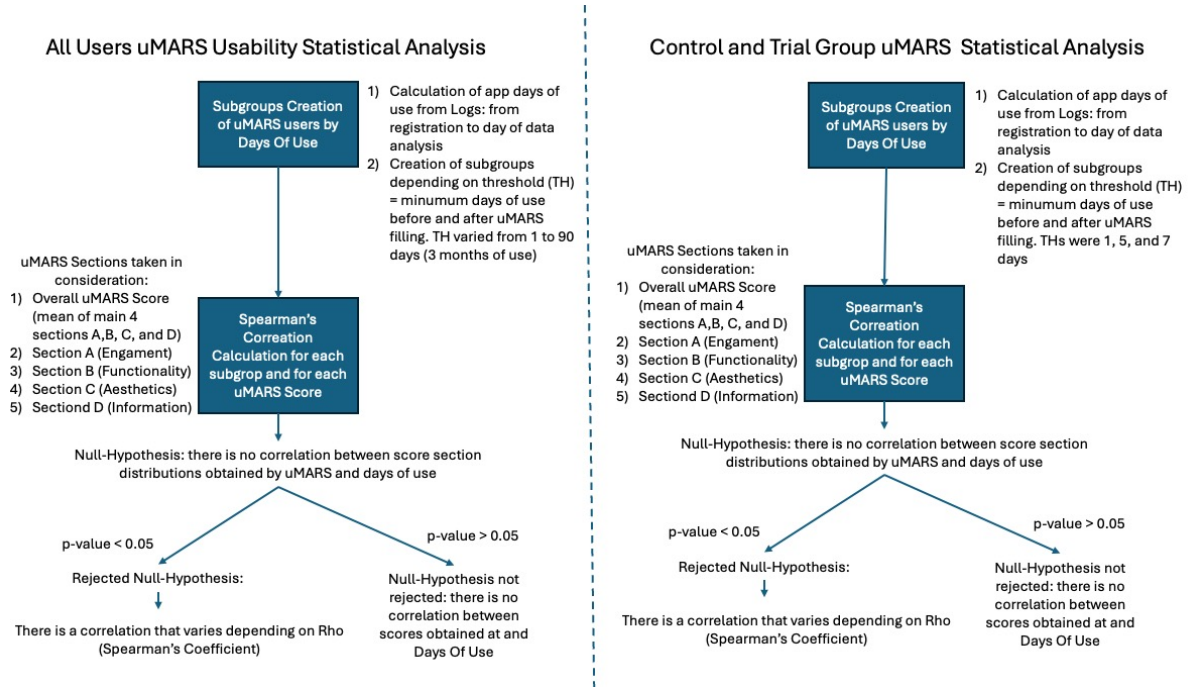

Figure 49: Statistical analysis procedure. On the left, the Spearman's correlation between uMARS usability evaluations and app days of use for all users; on the right, the statistical analysis to compare the uMARS usability evaluations and days of use of control and trial groups

Finally, the Mann-Whitney U Test was implemented for testing the null hypothesis of no difference between the scores obtained, for the different cited sections, for the trial and control subgroups, with a TH equal to 7.

The Python function used for the Spearman's calculation was the stats.spearmanr with arguments (x_values, y_values), resulting in rho correlation coefficient, between -1 and +1, and the related p-value, while the Python function used for the Mann-Whitney calculation was the stats.mannwhitney, with arguments (control_group_item_scores, trial_group_item_scores, alternative='less'), calculated for each score section. The stats methods are part of Python scipy.stats library, version 1.15.3.

The relevance of the output of this analysis was focused on the impact that the uMARS sections and items have revealed about the ability of the BRCApp to provide suggestions and contents to improve the user's healthy behavior and lifestyle, as well as on the general user's satisfaction that relies on the autonomous app use in a real-word use case.

The user's comments were extracted from the last 27th uMARS item, and manually scrutinized to correct and understand the UI- and UX-related technical problems and bugs, but they were not reported for the purpose of this analysis.

3.3. Results

From the beginning of the study (28th June 2024), 1546 users registered to the BRCApp, of which 81 accounts were testers, which were not considered, and 147 accounts were found as duplicates of users, that deleted and recreated their credentials, thus resulting in a total number of 1318 unique recruited volunteers.

The usability study started on 18th February 2025, and it is currently undergoing. The data for the presented analysis were extracted on 30th December 2025.

Among all the registered e-Brave study participants, 110 users have filled-in the uMARS questionnaire, and 59 of them were randomly assigned to control group, while 36 assigned to the trial.

3.3.1. Usability Results of the entire group

Table 6 represents in detail the different scores that are typically calculated to evaluate the uMARS general results, while Figure 50 shows such results a boxplot, with the different mean and median values for each section to be visually comparable. It is already possible to notice quite a difference between the tendence of the distributions for the items of section D in respect to the others, highlighting the importance of the related information contents, which is the main BRCApp functionality of the eBrave study intervention.

For completeness, Table B 1 reports the median values obtained for each uMARS questionnaire item. Here, it is possible to observe that the 19th item, asking to the users if they are willing to pay for the BRCApp, reported the worst median score equal to 1.00 (1.00;2.00). This general negative answer was expected, being the BRCApp conceived for research purpose. Instead, the item 16 obtained the best median score of 5.00 (5.00;5.00). This result represents an optimum initial goal, being the app designed to provide principally lifestyle suggestions, i.e., information to improve user's healthy lifestyle. Indeed, this item is part of the D Information Section, that asks to the users if the contents and suggestions about this context are reliable, underling the trust that the users gave to this app.

Table 6: Overall uMARS score and its value for each section, including objective and subjective quality, and perceived impact, expressed as Mean and Standard Deviation (SD) as well as Median with 25th and 75th percentiles (25th;75th)

Measure	Mean (SD)	Median (25th;75th)
Overall uMARS Score = Objective Quality	3.56 (0.69)	4.00 (3.00;4.00)
Section A Score (Engagement)	3.31 (1.02)	3.00 (3.00;4.00)
Section B Score (Functionality)	3.51 (0.94)	4.00 (3.00;4.00)
Section C Score (Aesthetics)	3.51 (0.82)	4.00 (3.00;4.00)
Section D Score (Information)	3.92 (1.05)	4.00 (3.00;5.00)
Section E Score (Subjective Quality)	3.14 (1.29)	3.00 (2.00;4.00)
Section F Score (Perceived Impact)	3.18 (1.20)	3.00 (2.00;4.00)

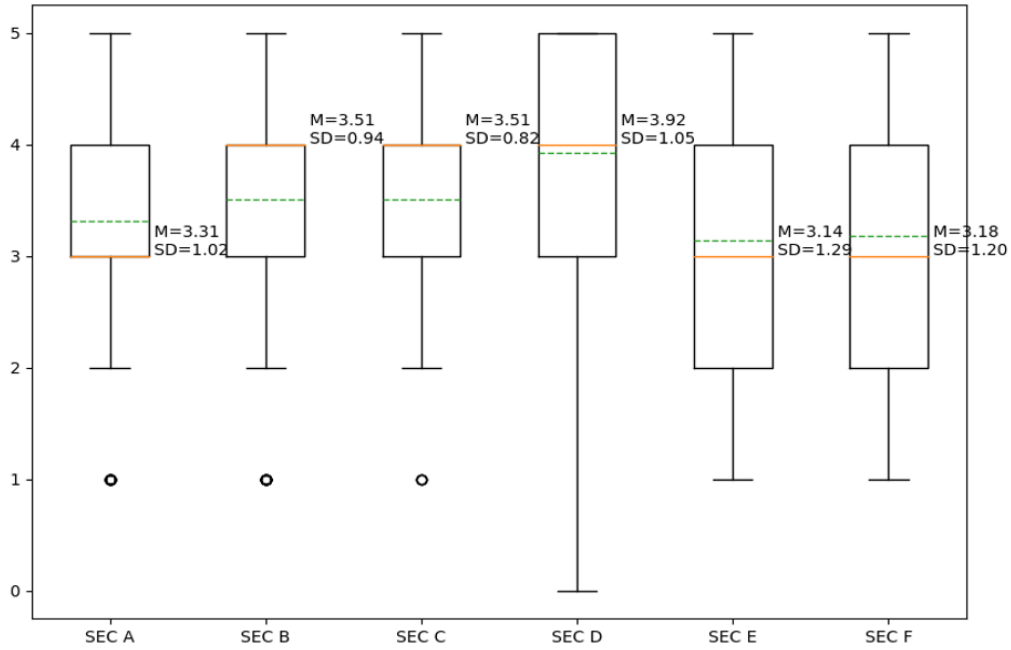

Figure 50: Boxplot representing the scores of the different section (SEC A = Engagement, SEC B = Functionality, SEC C = Aesthetics, SEC D = Information, SEC E = Subjective Quality, SEC F = Perceived Impact). The green dotted lines represent the mean, while the red ones the median values.

The Figure 51, Figure 52, Figure 53, Figure 54, and Figure 55, flanked by the Table 7, show the Spearman's Correlation results calculated on the entire sample size without the users the stopped to use the app after uMARS filling, which resulted in just one (TH=1 and n=109). The Spearman's Correlations were calculated between each of the different scores given by the different uMARS sections, the Overall uMARS Score as the mean of the main four sections (A, B, C, and D), and the scores for each of these main sections, and the Days of Activity.

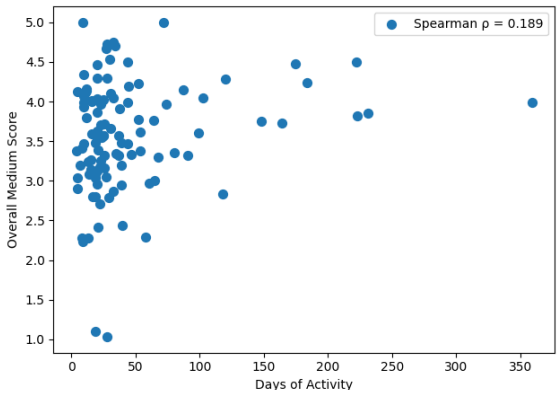

Figure 51: Overall uMARS Score (mean of the main four sections A, B, C, and D) vs Days of Activity resulting in a RHO = 0.189 with a p-value = 0.049, with TH=1 (n=109)

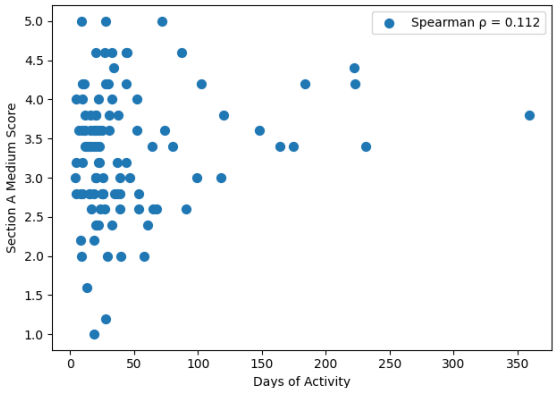

Figure 52: Section A (Engagement) vs Days of Activity resulting in a RHO = 0.112 with a p-value = 0.244, with TH=1 (n=109)

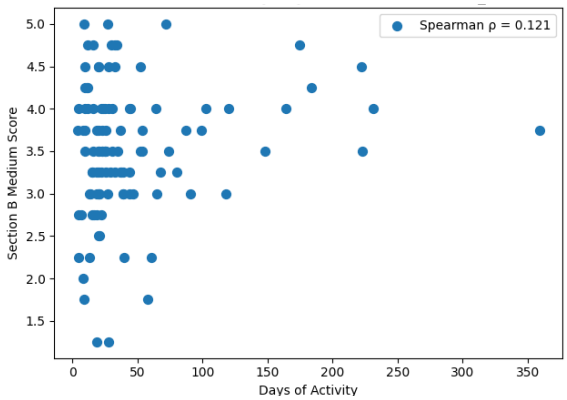

Figure 53: Section B (Functionality) vs Days of Activity resulting in a RHO = 0.121with a p-value = 0.211, with TH=1 (n=109)

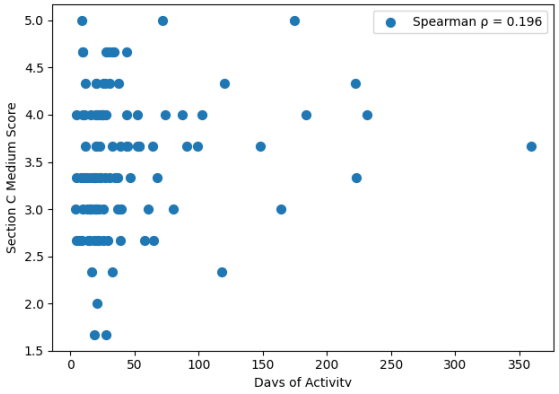

Figure 54: Section C (Aesthetics) vs Days of Activity resulting in a RHO = 0.196 with a p-value = 0.0408, with TH=1 (n=109)

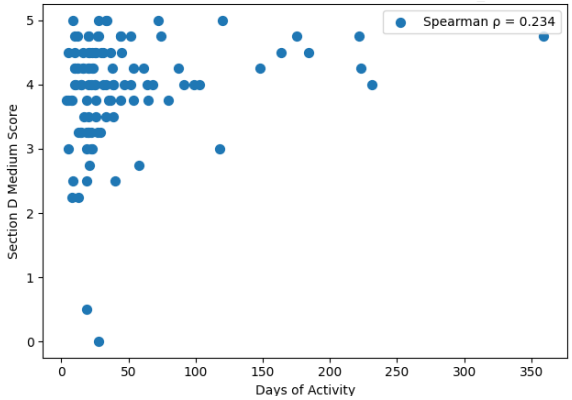

Figure 55: Section D (Aesthetics) vs Days of Activity resulting in a RHO = 0.234 with a p-value = 0.0142, with TH=1 (n=109)

Table 7: summary of Spearman's Correlation Coefficients (RHO and p-values) with TH = 1 and n=109. The Section D showed a light positive statistically significant correlation with RHO = 0.234 and a p-value < 0.05

Spearman's Correlation	Rho	p-value
Overall uMARS Score = Objective Quality	0.189	0.049
Section A Score (Engagement)	0.112	0.244
Section B Score (Functionality)	0.121	0.211
Section C Score Mean (Aesthetics)	0.196	0.041
Section D Score Mean (Information)	0.234	0.014

These results indicate that there was a significant correlation between the Overall uMARS Score, the Section C, and the Section D, and the Days of Activity.

These initial results reinforce the idea that increasing the app use (Days of Activity), the scores increase consequently. Moreover, the Section D (Information) obtained a slightly positive statistically significant correlation, that confirmed the importance of the information functionalities, such as the dietary o physical activity suggestions and contents presented to the users through the BRCApp, which is one of the main interventions to the app users.

Figure 56, Figure 57, Figure 58, Figure 59, Figure 60, and Table 8, represent the Spearman's Correlation calculated for the subgroup with a TH = 5, thus considering only the users with a minimum of 5 activity days, before and after the uMARS administration. The TH = 5 resulted in a subgroup n = 72.

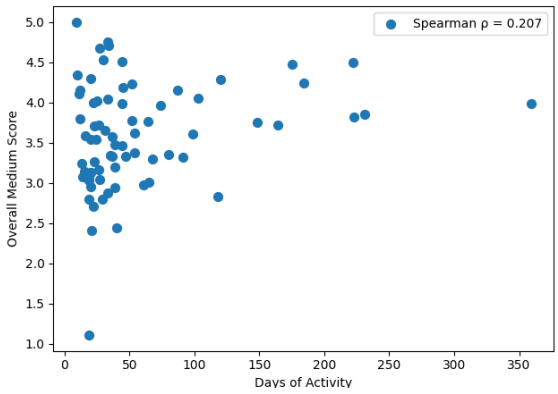

Figure 56: Overall uMARS Score (mean of the main four sections A, B, C, and D) vs Days of Activity resulting in a RHO = 0.207 with a p-value = 0.082, with TH=5 (n= 72)

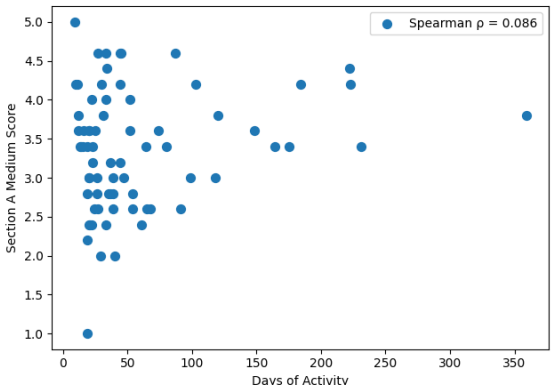

Figure 57: Section A (Engagement) vs Days of Activity resulting in a RHO = 0.086 with a p-value = 0.474, with TH=5 (n= 72)

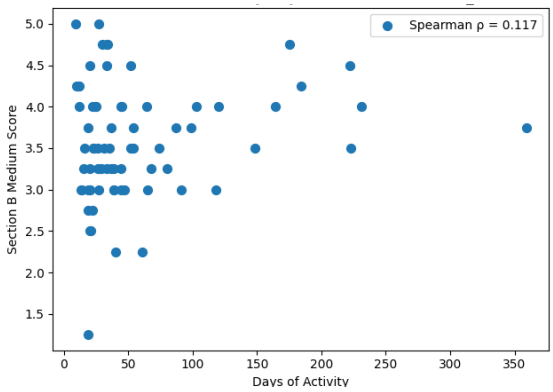

Figure 58: Section B (Functionality) vs Days of Activity resulting in a RHO = 0.117 with a p-value = 0.33, with TH=5 (n= 72)

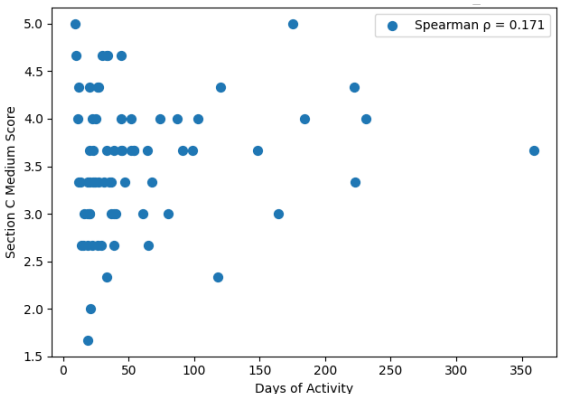

Figure 59: Section C (Aesthetics) vs Days of Activity resulting in a RHO = 0.171 with a p-value = 0.151, with TH=5 (n= 72)

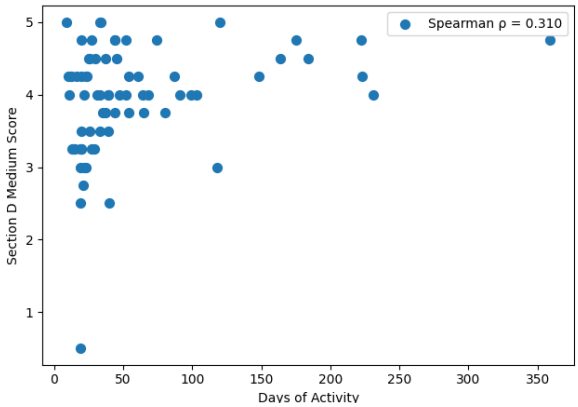

Figure 60: Section D (Aesthetics) vs Days of Activity resulting in a RHO = 0.310 with a p-value = 0.008, with TH=5 (n= 72)

Table 8: summary of Spearman's Correlation Coefficients (RHO and p-values) with TH = 5 and n=72. Only the D shows a statistically significant correlation with a p-value<0.05, while all the other scores obtained slight positive correlations, but not significant.

Spearman's Correlation	Rho	p-value
Overall uMARS Score vs Activity Days	0.207	0.082
Section A Score (Engagement) vs Activity Days	0.086	0.474
Section B Score (Functionality) vs Activity Days	0.117	0.33
Section C Score Mean (Aesthetics) vs Activity Days	0.171	0.151
Section D Score Mean (Information) vs Activity Days	0.310	0.008

These results indicate that, passing from TH = 1 to TH = 5, the Section D has maintained a statistically significant correlation, incrementing the RHO as well from 0.234 to 0.310. Only the Overall uMARS score obtained a p-value close to 0.05, augmenting the RHO value to 0.207 as well. This happened dropping the less active users, demonstrating a higher usability score for the users that spent more days on the BRCApp, in particular for Section D.

Continuing, the Figure 61, Figure 62, Figure 63, Figure 64, Figure 65, and the Table 9 show the results passing from TH = 5 and TH = 7, with a sample size n = 58.

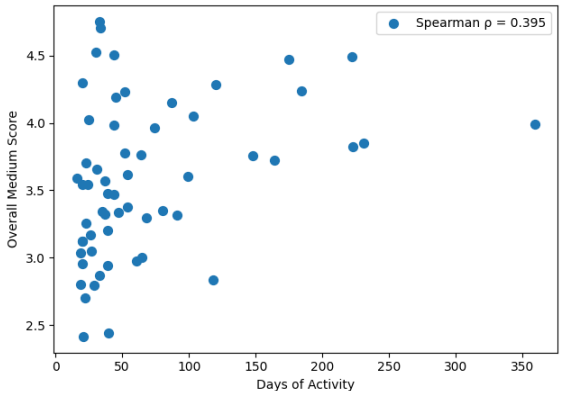

Figure 61: Overall uMARS Score (mean of the main four sections A, B, C, and D) vs Days of Activity resulting in a RHO = 0.395 with a p-value = 0.002, with TH=7 (n=58)

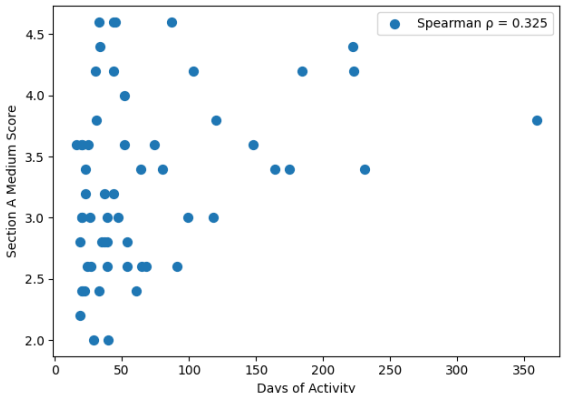

Figure 62: Section A (Engagement) vs Days of Activity resulting in RHO = 0.325 with a p-value = 0.013, with TH=7 (n=58)

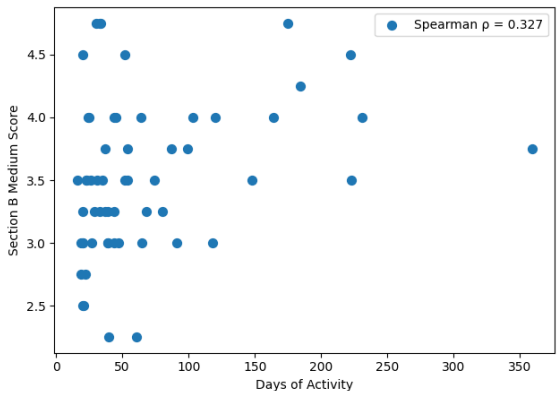

Figure 63: Section B (Functionality) vs Days of Activity resulting in RHO = 0.327 with a p-value = 0.012, with TH=7 (n=58)

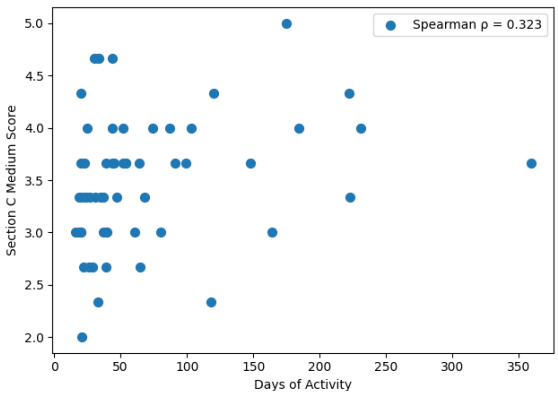

Figure 64: Section C (Aesthetics) vs Days of Activity resulting in a RHO = 0.323 with a p-value = 0.013, with TH=7 (n=58)

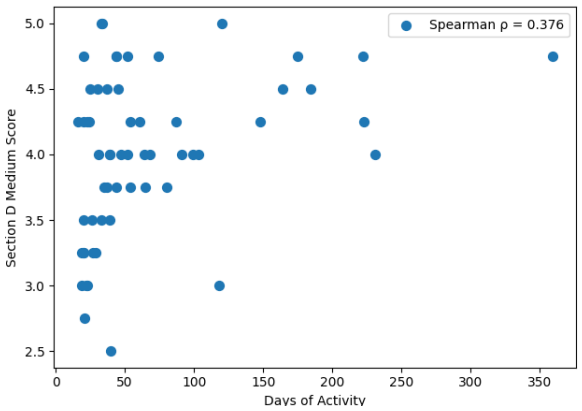

Figure 65: Section D (Information) vs Days of Activity resulting in a RHO = 0.376 with a p-value = 0.003, with TH=7 (n=58)

Table 9: summary of Spearman's Correlation Coefficients (RHO and p-values) with TH = 7 and n=58.

Spearman's Correlation	Rho	p-value
Overall uMARS Score vs Activity Days	0.395	0.002
Section A Score (Engagement) vs Activity Days	0.325	0.013
Section B Score (Functionality) vs Activity Days	0.327	0.012
Section C Score Mean (Aesthetics) vs Activity Days	0.323	0.013
Section D Score Mean (Information) vs Activity Days	0.376	0.003

Considering only the users with at least 1 week of activity before and after the usability evaluation, the Spearman's Correlation increased the significance and RHO values for all sections. This result confirmed what we expected: increasing the Days of Activity of the users, the usability increased, followed by a higher reliability of the results (p-values < 0.05). Indeed, the Section A, representing the Engagement, is slightly increasing with the increase of active days of the users, that were more engaged than the dropped users from the subgroups. Section D confirmed its significance in the usability results. In this analysis, all the BRCApp users were included, thus, without distinguishing from normal, control, and trial users. Indeed, the e-Brave study provided to control and trial users different lifestyle suggestions and contents, while the normal users, which were not tagged as control or trial, did not receive any additional lifestyle contents (see Figure 48).

Finally, Figure 66, Figure 67, Figure 68, Figure 69, and Figure 70, show the trends of the RHO correlation coefficients calculated for each of the same scores passing from TH = 1 to TH = 90, giving the visualization of the behaviour of RHO and the threshold after which is lost the significance (p-value<0.05, represented by green dots, and no points where correlation was not calculable).

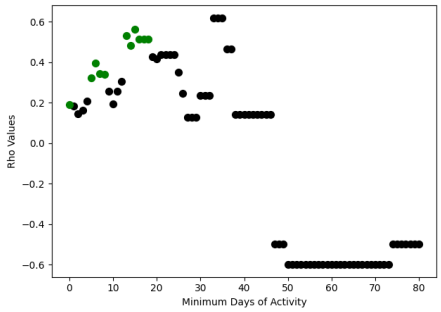

Figure 66: different RHO correlation coefficients calculated between the Overall uMARS Scores and the different Minimum Active Days of Activity from TH = 1 to TH = 90 (p-value<0.05 are represented by green dots)

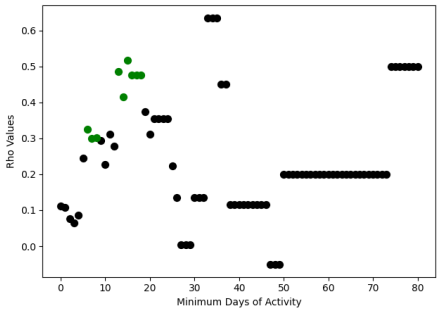

Figure 67: different RHO correlation coefficients calculated between the Section A Scores and the different Minimum Active Days of Activity from TH = 1 to TH = 90 (p-value<0.05 are represented by green dots)

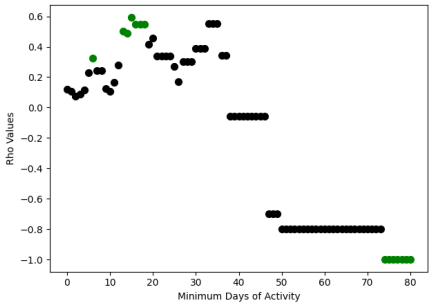

Figure 68: different RHO correlation coefficients calculated between the Section B Scores and the different Minimum Active Days of Activity from TH = 1 to TH = 90

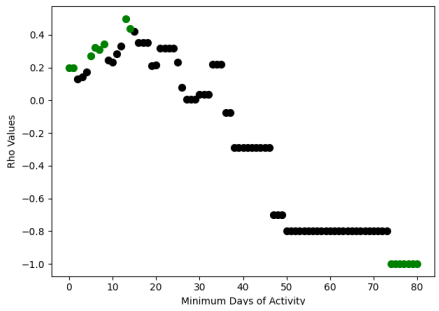

Figure 69: different RHO correlation coefficients calculated between the Section C Scores and the different Minimum Active Days of Activity from TH = 1 to TH = 90 (p-value<0.05 are represented by green dots)

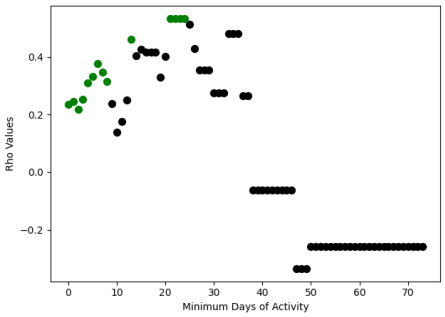

Figure 70: different RHO correlation coefficients calculated between the Section D Scores and the different Minimum Active Days of Activity from TH = 1 to TH = 90 (p-value<0.05 are represented by green dots)

From these results, it is confirmed how in general the correlations reached significant values, increasing RHO values as well, by increasing the TH, i.e., by excluding the users that used less the app. This is coherent with the idea that the effective usability satisfaction increases hand in hand with the Days of Activity. It can also be noticed that the statistical significance of the correlations was lost with a TH of around 20 days of activity, due to the significant decreasing of sample sizes after that threshold. Moreover, the result of the Section D is following the initial hypothesis that the BRCApp use is particularly influenced by the Information module. Indeed, the informative contents about lifestyle and physical activities are given during the use of the app, maintaining the satisfaction about this section high.

3.3.2. Usability Results from comparison of trial and control groups

The same statistical process applied to the entire group (n=110) was applied to compare the two randomized subgroups: the control (n= 59) and trial (n= 36) groups.

Figure 71, Figure 72, Figure 73, Figure 74, and Figure 75, show the results obtained calculating the Spearman's Correlation with a TH = 1, with sample sizes of 58 and 36 for control and trial subgroups, respectively, then, losing just one user in the trial group that has never opened the app after the uMARS filling. The correlations were calculated for each of the different scores: the Overall uMARS, the Section A, B, C, and D. The figures indicate the control users with blue dots, while the trial users with red dots. The Table 10 summarizes these results.

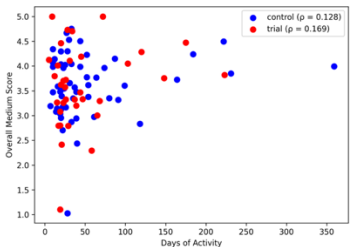

Figure 71: Spearman's Correlation Coefficients calculated between the Overall uMARS Scores and the Days of Activity for TH = 1. The blue dots represent the control group (n=58), with a RHO = 0.128 and a p-value = 0.339, while the red dots represent the trial group (n=36), with a RHO = 0.169 and a p-value = 0.324

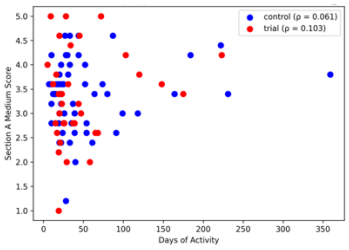

Figure 72: Spearman's Correlation Coefficients calculated between the Section A Scores and the Days of Activity for TH = 1. The blue dots represent the control group (n=58), with a RHO = 0.061 and a p-value = 0.649, while the red dots represent the trial group (n=36), with a RHO = 0.103 and a p-value = 0.551

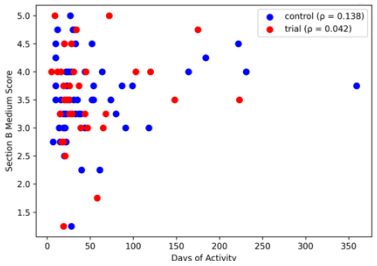

Figure 73: Spearman's Correlation Coefficients calculated between the Section B Scores and the Days of Activity for TH = 1. The blue dots represent the control group (n=58), with a RHO = 0.138 and a p-value = 0.3, while the red dots represent the trial group (n=36), with a RHO = 0.042 and a p-value = 0.807

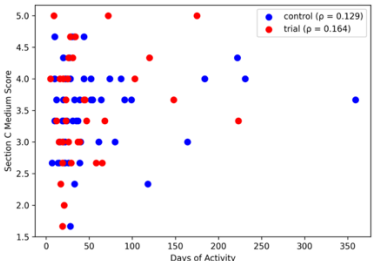

Figure 74: Spearman's Correlation Coefficients calculated between the Section C Scores and the Days of Activity for TH = 1. The blue dots represent the control group (n=58), with a RHO = 0.129 and a p-value = 0.335, while the red dots represent the trial group (n=36), with a RHO = 0.164 and a p-value = 0.339

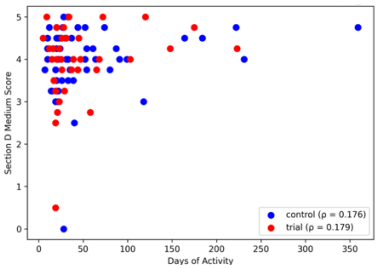

Figure 75: Spearman's Correlation Coefficients calculated between the Section C Scores and the Days of Activity for TH = 1. The blue dots represent the control group (n=58), with a RHO = 0.176 and a p-value = 0.186, while the red dots represent the trial group (n=36), with a RHO = 0.179 and a p-value = 0.296

Table 10: summary of Control (n=58) and Trial (n=36) subgroups Spearman's Correlation Coefficients and their p-values for TH = 1. They didn't show any statistical significance.

Spearman's Correlation	Rho Control	p-value Control	Roh Trial	p-value Trial
Overall uMARS Score vs Activity Days	0.128	0.339	0.169	0.324
Section A Score (Engagement) vs Activity Days	0.061	0.649	0.103	0.551
Section B Score (Functionality) vs Activity Days	0.138	0.3	0.042	0.807
Section C Score Mean (Aesthetics) vs Activity Days	0.129	0.335	0.164	0.339
Section D Score Mean (Information) vs Activity Days	0.176	0.186	0.179	0.296

No significant correlations between the usability scores and the days of activity was found for both groups. This could be expected considering the entire control and trial groups with TH = 1 (Table 7). Indeed, this comparison included also the users that used the app few days, impacting the correlations and the significance of the results. However, Section D (Information) is already showing, albeit weakly, higher correlation values, both for control and trial, compared to the other sections.

Then, the same analysis was extended for TH=5, represented by the Figure 76, Figure 77, Figure 78, Figure 79, Figure 80, and Table 11, between the control (n=45) and trial (n=23) subgroups.

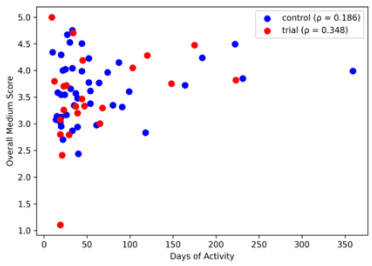

Figure 76: Spearman's Correlation Coefficients calculated between the Overall uMARS Scores and the Days of Activity for TH = 5. The blue dots represent the control group (n=45), with a RHO = 0.186 and a p-value = 0.222, while the red dots represent the trial group (n=23), with a RHO = 0.348 and a p-value = 0.104

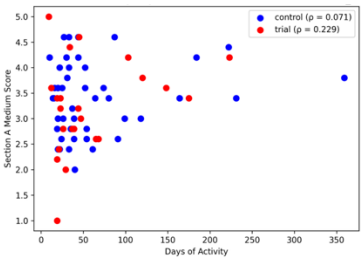

Figure 77: Spearman's Correlation Coefficients calculated between the Section A Scores and the Days of Activity for TH = 5. The blue dots represent the control group (n=45), with a RHO = 0.071 and a p-value = 0.643, while the red dots represent the trial group (n=23), with a RHO = 0.229 and a p-value = 0.292

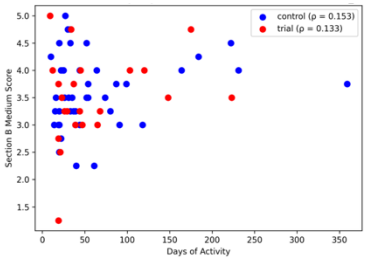

Figure 78: Spearman's Correlation Coefficients calculated between the Section B Scores and the Days of Activity for TH = 5. The blue dots represent the control group (n=45), with a RHO = 0.153 and a p-value = 0.316, while the red dots represent the trial group (n=23), with a RHO = 0.133 and a p-value = 0.544

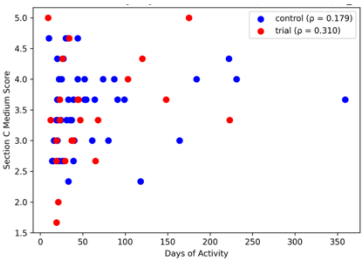

Figure 79: Spearman's Correlation Coefficients calculated between the Section C Scores and the Days of Activity for TH = 5. The blue dots represent the control group (n=45), with a RHO = 0.179 and a p-value = 0.239, while the red dots represent the trial group (n=23), with a RHO = 0.310 and a p-value = 0.151

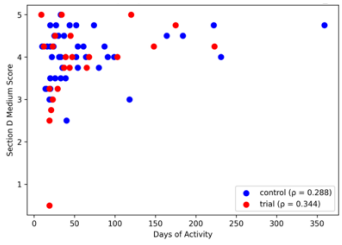

Figure 80: Spearman's Correlation Coefficients calculated between the Section D Scores and the Days of Activity for TH = 5. The blue dots represent the control group (n=45), with a RHO = 0.288 and a p-value = 0.055, while the red dots represent the trial group (n=23), with a RHO = 0.344 and a p-value = 0.108

Table 11: summary of Control (n=45) and Trial (n=23) subgroups Spearman's Correlation Coefficients and their p-values for TH = 5. No sections show significant correlations.

Spearman's Correlation	Rho Control	p-value Control	Roh Trial	p-value Trial
Overall uMARS Score vs Activity Days	0.186	0.222	0.348	0.104
Section A Score (Engagement) vs Activity Days	0.071	0.643	0.229	0.292
Section B Score (Functionality) vs Activity Days	0.153	0.316	0.133	0.544
Section C Score Mean (Aesthetics) vs Activity Days	0.179	0.239	0.310	0.151
Section D Score Mean (Information) vs Activity Days	0.288	0.055	0.344	0.108

Despite a general increase in correlation values, no sections showed significant correlations.

Finally, the Spearman's correlation was evaluated for TH = 7, and Figure 81, Figure 82, Figure 83, Figure 84, Figure 85, and Table 12, show these results, with sample sizes of n=39 and n=18 for control and trial subgroups, respectively.

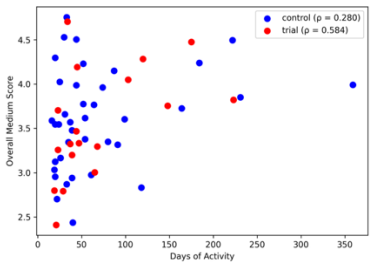

Figure 81: Spearman's Correlation Coefficients calculated between the Overall uMARS Scores and the Days of Activity for TH = 7. The blue dots represent the control group (n=39), with a RHO = 0.280 and a p-value = 0.085, while the red dots represent the trial group (n=18), with a RHO = 0.584 and a p-value = 0.011 (<0.05)

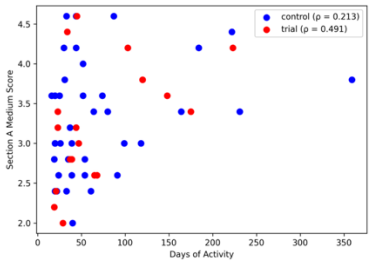

Figure 82: Spearman's Correlation Coefficients calculated between the Section A Scores and the Days of Activity for TH = 7. The blue dots represent the control group (n=39), with a RHO = 0.213 and a p-value = 0.193, while the red dots represent the trial group (n=18), with a RHO = 0.491 and a p-value = 0.039 (<0.05)

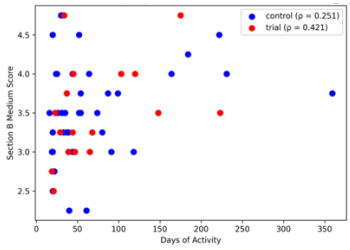

Figure 83: Spearman's Correlation Coefficients calculated between the Section B Scores and the Days of Activity for TH = 7. The blue dots represent the control group (n=39), with a RHO = 0.251 and a p-value = 0.123, while the red dots represent the trial group (n=18), with a RHO = 0.421 and a p-value = 0.082

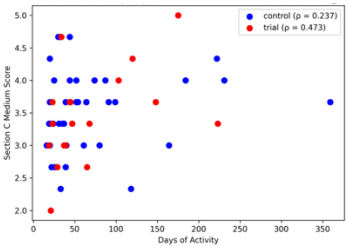

Figure 84: Spearman's Correlation Coefficients calculated between the Section C Scores and the Days of Activity for TH = 7. The blue dots represent the control group (n=39), with a RHO = 0.237 and a p-value = 0.146, while the red dots represent the trial group (n=18), with a RHO = 0.473 and a p-value = 0.047 (<0.05)

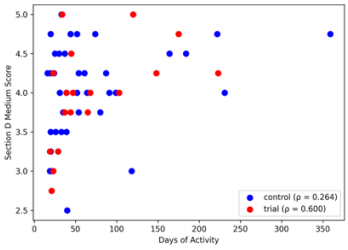

Figure 85: Spearman's Correlation Coefficients calculated between the Section D Scores and the Days of Activity for TH = 7. The blue dots represent the control group (n=39), with a RHO = 0.264 and a p-value = 0.104, while the red dots represent the trial group (n=18), with a RHO = 0.600 and a p-value = 0.008 (<0.05)

Table 12: summary of Control (n=39) and Trial (n=18) subgroups Spearman's Correlation Coefficients and their p-values for TH = 7. Practically, all the sections for the trial subgroup showed statistically significant positive correlations and a RHO value for the Section D close to 1.

Spearman's Correlation	Rho Control	p-value Control	Rho Trial	p-value Trial
Overall uMARS Score vs Activity Days	0.280	0.085	0.584	0.011
Section A Score (Engagement) vs Activity Days	0.213	0.193	0.667	0.039
Section B Score (Functionality) vs Activity Days	0.251	0.123	0.543	0.082
Section C Score Mean (Aesthetics) vs Activity Days	0.237	0.146	0.445	0.047
Section D Score Mean (Information) vs Activity Days	0.264	0.104	0.727	0.008

As predicted, the Section D Score demonstrated the highest contribute to the use of the BRCApp in the Trial group, with a strong correlation of 0.727. Indeed, the Section D score seemed to weight more than the other sections, in line with the concept of the e-Brave study of treating the users by enriching the showed information contents with dietary and physical activity suggestions.
Moreover, it's possible to notice how the trial subgroup obtained the highest correlations values, supporting the hypothesis that the treatment through BRCApp was perceived positively by the users and thus transformed in an active use of the app.

At last, the Mann-Whitney U Test was computed between the control and trial group scores for the TH = 7 case, for each of the section scores.

Table 13: Mann-Whitney U Test for the different uMARS section scores between control and trial groups for TH=7

Section Score	U	p-value
Overall uMARS Score vs Activity Days	1035.5	0.566
Section A Score (Engagement) vs Activity Days	1106.0	0.767
Section B Score (Functionality) vs Activity Days	985.0	0.407
Section C Score Mean (Aesthetics) vs Activity Days	984.0	0.403
Section D Score Mean (Information) vs Activity Days	1051.0	0.615

No statistically significant p-values were obtained (Table 13); thus, this analysis didn't catch any differences between the subgroups. Nevertheless, this result does not disprove the correlation results described previously.

3.4. Discussions and Conclusions

The e-Brave study has represented the best example of a real-world use case involving LC Ecosystem to provide a health & wellness service targeted to improve the end-user condition through the use of RWD collected in form of self-reported data (such as questionnaires, and physiological parameters) by the BRCApp mobile app.
This usability study conducted by administering directly the uMARS questionnaire to the end-users represents a replicable practice that can be applied to all the others mobile apps based upon LC Ecosystem, giving the possibility to understand the user's satisfaction in different real-world use cases.
This approach represents a novelty in the analysis of mobile app's usability. Indeed, there are no other studies in literature (see Table 1) that investigated it by comparing the real-world effective app usage, obtained through the app Logs, to the calculated scores of usability questionnaires, administered directly through the mobile app, for a reasonable amount of time (not just a first user's interaction or demo). In this way, the proposed analysis provides a snapshot of the real app usability perception in a real-world setting, because obtained by letting the users to use the app autonomously,

without any influence or external help. Mathematically, the correlations between the app usability scores and the effective amount of app usage (here calculated as "days of use") can be used as a tool to understand if the general user's satisfaction is following the expected effective real-world use, reinforcing the truthfulness of the results. This is particularly important because these results will constitute the knowledge base for future implementations to improve the mobile app and the platform following an Agile logic as DevOps cycle (see Chapter 1).

Moreover, the use of the uMARS questionnaire adds the possibility to investigate the mobile app usability in its different aspects, through different sections, such as the user's engagement (Section A), the functionalities (Section B), the aesthetics (the Section C), the information (Section D), and the perceived subjective impact (Section E) of the tool. As described, the information and contents provided through the BRCApp represented one of the main means to dispense pills and suggestions to improve the end-user's eBrave study outcomes, such as the monitoring and improvement of weight and abdominal circumference, following diets and physical exercises suggestions. Thus, the obtained scores of uMARS information section became important, because a high or low level of acceptance could influence positively or negatively, respectively, the use and understanding of these informative contents provided by the BRCApp, thus, influencing positively or negatively the outcome of the eBrave study. From these conclusions, the score obtained by the information section represented a good starting point to expect a positive final result, beyond a high overall score of the app (Table 6).

In addition, it could be noticed from TH analysis that the engagement positively impacted on the usability results, increasing the Spearman's correlation RHO values and the significance of the analysis at the increasing of TH. This can be considered coherent with the results, because an user that continued to use the app for long time implicitly demonstrated more engagement, thus, probably more satisfaction in using the BRCApp. For this reason, users that at the beginning of the usability study were already using the app for an amount of time greater than one week could skewed in a positive direction the usability results, obtaining higher scores for the different sections than the users that filled in the uMARS questionnaires after just one week of use.

Finally, this study pioneers to the possibility of using the mHealth-based LifeCharger Ecosystem for other cohort studies. Indeed, the flexibility of the developed platform allows to configure paths and tools that are needed to conduct cohorts for different scenarios. The tags that can be created with the version 2.0 of LifeCharger's System (The Data Processing – Tag Routine) allow to create different pipelines for the users inside different studies, while the possibility to administer questionnaires, create ad-hoc profiles, and acquire parameters allows to set different outcomes depending on different cohort's purposes. An example of this flexibility can be explored by imagining to adapt this solution to the Telewear platform of [5], cited in Table A 7 and

in paragraph 1.4.2. The Telewear project, to study atrial fibrillation effects on their patients, administered as primary PRO tool the Atrial Fibrillation Effect on QualiTy-of-life Questionnaire (AFEQT), and other PROMs to include Patient Reported Outcomes Measurement Information System (PROMIS) Global Health and Patient Health Questionnaire-2 (PHQ-2); in addition to provide electrocardiograms every two weeks. The SynCare platform offers to the researchers the possibility to insert each type of questionnaires, and to the users the possibility to add its own medical reports through the "Documents" section. Moreover, for this type of study, where researchers conduct RCTs to validate the proposed solution, the Syncare platform represents a perfect tool to embed all the necessary passages to set up the environment: embedded informed digital consents; patients' time points configured through tags module, with the possibility to randomize users to adapt the app to the different branches (see Figure 48), adjustable PROMS; notifications and contents to help the users during their journey; etc…

4 Conclusions

This thesis addressed key challenges in understanding RWD characteristics to develop a mobile-based RWD platform that can collect, manage and exploit these types of data to provide to the end-users the best health & wellness service possible, while maintaining a certain quality and security of data during the whole life cycle, using best practices and frameworks. RWD are crucial for obtaining RWE that can be used as insights to improve the outcome of the provided health & wellness services, through the mHealth apps in the end-user's hands.

By leveraging on different development frameworks and innovative technologies such the blockchain, a secure mHealth-based RWD platform was developed and secured, to provide to the end-users different types of health & wellness services, enhanced and fed by their own personal self-reported data.
The architecture was designed to be scalable, flexible, and applicable in different real-world use cases. Indeed, the platform has demonstrated the ability to be used in a prospective cohort study, the e-Brave study [78], by collecting different types of self-reported data, such as questionnaires and physiological parameters, monitoring the end-user's behaviours and trends, during the app utilization. In addition, the informed digital consents was signed directly through the mHealth app and saved as a smart contract on the Ethereum public blockchain, creating a secure and not tamperable consent ledger, recoverable in each moment, ensuring that the mHealth app could share sensitive data for that purpose [43].

Below, we summarize the key findings, and limitations, based on the results of this work.

4.1. Key Findings

1. How Real World Data (RWD) are defined across various entities and in literature? What are the sources of RWD, and is mHealth a privileged source to collect RWD? What are the features that compose and affect RWD quality? What are the tools and frameworks used to manage and maintain RWD quality along their lifecycle?

A non-systematic literature review was done to scrutinize the variety of definitions of RWD across various entities. The RWD definitions were found to vary based on their context of use, ranging from observational data generated during routine healthcare

provision, to patient-generated health data (PGHD) collected through mobile apps and wearables.

RWD can be viewed as observational user health-related data reflecting actual healthcare encounters, both collected passively and actively. Importantly, this definition aligns with the passive or active collection of health data via digital tools, devices, wearables, or apps, but the Food and Drugs Administration (FDA) definition is the most frequently cited, and it also underlines the use of digital health technologies, such as mobile health apps, to gather health-related data. The FDA defines RWD in 2017 as "*data related to patient health status and/or the delivery of health care routinely collected from Electronic Health Records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices*". These last words emphasized the role of mHealth as RWD source, to capture data ubiquitously and integrate them with other sources, such as Electronic Health Records (EHRs), wearables, sensors, and additional apps.

In the role of managing data within its life cycle, quality has revealed to be a property crucial for the effective use of RWD. High-quality RWD is defined as data that are "*intrinsically good, contextually appropriate, clearly represented, and accessible to data consumers*", manifested through key features across different phases of data life cycle. We observed that these features can be divided into:

1) intrinsic features, important in the Data Acquisition phase of the lifecycle, composed by completeness (the extent to which missing data about the user are present), correctness/accuracy/reliability (how accurately the data values reflect reality), and heterogeneity (assessing the variability in the same type of data among different users, depending on the source of data acquisition), to maintain timeliness (data can be requested to the users and updated when is needed), and relevancy (data sample of interest is presentiveness of demographic characteristics);

2) contextual or extrinsic features, along with the Data Management phase of RWD lifecycle, represented by confidentiality (storage to protect sensitive information from unauthorized access), integrity (ensuring data integrity involves preventing accidental modifications), availability/timeliness (timely access to data for analysis), and authenticity (provenance documentation);

3) technical features, throughout the entire life cycle, ensuring traceability and interoperability leveraging on interoperability standards to ensure that RWD collected in various healthcare settings can be seamlessly shared.

We explored different frameworks to ensure and maintain the different RWD properties for quality within the life cycle. Examples are based on the Control Objectives for Information and related Technology (COBIT) framework, or ISO 27001 standard, or more the Harmonized Intrinsic DQ framework (HIDQF), aiming at identifying DQ properties and terminology. We reported open-source tools that

mainly address intrinsic DQ indicators, or even the ATRAcT (Authentic Transparent Relevant Accurate Track-Record) framework, a sort of questionnaire that can be used to verify that the data sources follow some properties inside the mentioned dimensions, enhancing the quality of RWD, in particular in the "Data Acquisition" phase of life cycle.

2. How mHealth can improve the collection and the quality of RWD, thus improving RWE? What are the features that compose and affect mHealth quality? What are the existing frameworks to assess and evaluate its quality? What are the frameworks and best practices for their real development? What are the real-world use cases and examples of RWD mHealth-based platform architectures?

Thanks to their nature designed to run on smartphones, mHealth apps imbue the RWD collection process with the property of ubiquity. These apps, equipped with advanced technologies, could facilitate continuous data collection throughout the day, capturing real-time insights into users' health and behaviour. The ubiquity extends beyond the clinical setting, enabling a holistic understanding of individuals' health states in their natural environments. This continuous and context-rich data collection potentially enhances the granularity and depth of RWD.

Indeed, the advances in technology surrounding mHealth Apps enable seamless integration with various data sources, fostering synergies that enrich the overall dataset. Integration with EHRs, wearables, sensors, and other health-related apps could potentially create a comprehensive user health profile. This integrated approach can provide a holistic view of individuals' health experiences and outcomes, adding some details of patient's health history that routine healthcare databases with therapy and clinical diagnoses inevitably miss

One of the most critical properties faceted influencing the quality of mHealth Apps was the usability. Usability hinges on how effectively end-users, be they citizens, patients, caregivers, or healthcare professionals, can navigate and derive utility from the application. We extracted some factors to be considered in a usability assessment: intuitive navigation (interface should be intuitive, allowing users to easily access features and information); efficient task completion (users should be able to perform essential tasks efficiently within the app); accessibility (improving features for individuals with disabilities, ensuring inclusivity in its design); and user feedbacks (incorporating mechanisms for users to provide feedback about their experience).

We also extracted features that can be used to evaluate the quality of mHealth applications from a technical standpoint, involving privacy and security, ensuring the protection of user-sensitive information, using privacy considerations for including proper management of personal information and compliance with relevant regulations.
Moreover, interoperability (the app's ability to interoperate with other systems and data, such as electronic health records (EHR)), software performance (efficiency and

performance of the software directly contribute to the user experience), data sharing capabilities (crucial for an integrated digital ecosystem and compliance verification with standards and specifications to ensure effective interoperability), and Transparent and Clear Consent for Data Usage (clarity and transparency regarding the purposes of data) were found to be important features that affect mHealth app quality.

In the realm of mHealth applications, we discovered that economic factors also play a pivotal role in shaping user perceptions and app quality, such as understanding reimbursement impact (availability of reimbursement options); user engagement and incentives (economic incentives prove to be a powerful driver of user engagement); assessing value for money (users often evaluate mHealth apps based on the perceived value for money); considerations of accessibility and affordability (economic accessibility of mHealth apps, including factors like costs or subscription fees); and economic sustainability (examining the economic sustainability of an mHealth app is a critical dimension of quality assessment) .

Finally, we deduced that the quality of mHealth applications, which exploit RWD, is intricately linked to the use and quality of RWD they gather. This interdependence was highlighted by the following key considerations: quality indicators derived from RWD (data collected by mHealth apps serve as the foundation for various quality indicators); pre/post market surveillance (evaluation of RWD to evaluate mHealth apps beyond their initial launch); defining app purpose and data analysis (purpose of an mHealth app is intricately linked to the nature and quality of the RWD it collects); data quality across the life cycle (adhering to best practices for RWD management); and strategic utilization of RWD (strategic incorporation of RWD into the development and optimization of mHealth apps). Thus, the synergy between mHealth app quality and RWD underscored the significance of robust data practices, contributing to the effectiveness, reliability, and user trust in these digital health solutions.

To evaluate mHealth quality, various methods were found in literature, contingent on the specific property of mHealth Apps under consideration, such as: A/B Testing for Feature Comparison; System Usability Scale (SUS) Questionnaire; Mobile App Rating Scale (MARS); National Frameworks and Guidelines in different countries that employed distinct frameworks to evaluate app quality; APA App Evaluation Framework; Net Promoter Survey (NPS); CEN-ISO/TS 823904-2; mHealth Engagement framework evaluation for chronic users affected by diabetes using RWD collected by mHealth App.

In essence, the quality of mHealth apps was presented as a multifaceted construct, intricately tied to real-world usage, technical robustness, economic considerations, integration with RWD, and adherence to regulatory standards. The discussed tools and frameworks serve as invaluable resources for developers, healthcare professionals, and end-users seeking to navigate and contribute to this evolving landscape of mobile health technology.

In addition, we noticed that established medical device guidelines and regulations are integral to cultivating a perspective of mHealth quality. The adherence to these regulatory frameworks and medical device guidelines, such as the European Union (EU) Medical Device Regulation (MDR) 2017/745, or national frameworks (e.g. FAST TRACK in Germany), or international guidelines as well, not only signifies compliance but also encompasses several aspects that collectively enhance the overall quality of these digital health solutions.

Indeed, regulatory guidelines are often designed to address safety concerns associated with healthcare applications. This includes considerations for potential risks, adverse events, and mitigation strategies, all of which contribute to the overall safety and quality profile of mHealth apps (e.g. the MDR 2017/745). Compliance with guidelines and regulations enhances user trust and confidence. Users are more likely to engage with and rely on an mHealth app that demonstrates a commitment to meeting established standards, fostering a positive user experience.

The exploration of frameworks for mHealth app development produced as result the Patient and Public Involvement (PPI) Approach; the International Comparison of Evaluation Criteria, TeleWear-AF Project Workflow; SNApp Framework for Behavioral Health Research; Waterfall Framework for Systematic Development; CeHRes Roadmap for Human-Centered Design. We found broad range of recommendations and tools that can be used to develop a RWD system starting from the principle of security and privacy by design, underling the importance of securing systems that collect and manage personal-generated health data (PGHD), suggesting interesting best practices, such as end-to-end encryption, authentication methods, and policy compliance, but also complex techniques, such as homomorphic cryptography, differential privacy, blockchain use, etc., that together can be seen as a framework to maintain integrity and confidentiality of PGHD in RWD ecosystems.

At the end, two types of real-world scenarios were mainly considered: 1) the real-world implementation with a focus on managing RWD throughout its journey, and 2) an ecosystem centred around mHealth apps for the collection of RWD.

3. How to develop a secure and innovative user centric RWD mHealth-based platform for patient monitoring? How could this platform evolve in a more generalized system that provide health & wellness service?

Starting from the previous research results, a list of concepts, tools and frameworks for the development of a mHealth app-based RWD platform was drafted.

The design started from including the concepts of privacy and security by design process. Thus, by following a DevOps Agile process, the first version of LifeCharger mHealth-based RWD was built. This system was centred on the innovative technology obtained using the Ethereum blockchain smart contracts. This allowed to create a secure data sharing process to allow the connection between the end-user's and professionals that used RWD to monitor and provide health & wellness services

through the LifeCharger SynCare system. Moreover, the mHealth was equipped with AES and RSA algorithms to allow the best encryption of user's self-reported data. Subsequently, a second version of this platform was developed adding a Data Analytics module to effectively exploit and analyse RWD to extract the best RWE possible, providing enhanced health & wellness services to the end-users using the mHealth app. This was reached by creating different Python scripts, that were run on a computer used as a server deploying and running the scripts every day automatically at a programmed time (routine). These allowed to obtained cleaned and analyzed RWD from end-user self-reported data, that consequently allowed to extract improved RWE that could be used to monitor and return insights to the end-users regarding their behaviour on using the app, enhancing the user experience and the satisfaction in using the app, thus, the engagement and the usability of using the developed platform.

4. How can this new developed platform be evaluated by end-users in real world case scenarios? How can results of end-user's perceived usability evaluation be associated with real-world effective use? Does the perceived usability have a direct impact on real-world usage of the mHealth developed device?

The e-Brave study has represented the best example of a real-world use case involving LC Ecosystem to provide a health & wellness service targeted to improve the end-user condition through the use of RWD collected in form of self-reported data (such as questionnaires, and physiological parameters) by the BRCApp mobile app. This initial usability study conducted by administering directly the uMARS questionnaire to the end-users through the mobile app, represents a replicable practice that can be applied to all the others mobile apps based upon LC Ecosystem, giving the possibility to understand the user's satisfaction in different real-world use cases. In addition, we proposed a new method for analysis of mobile app's usability. Indeed, there are no other studies in literature (see Table 1) that investigated the usability by comparing the real-world effective app usage, obtained through the app Logs, to the calculated scores of usability questionnaires, administered directly through the mobile app, for a reasonable amount of time (not just a first user's interaction or demo). This analysis provides a snapshot of the real app usability perception in a real-world setting.

Moreover, the use of the uMARS questionnaire gave the possibility to investigate the mobile app usability through user's engagement (Section A), app functionalities (Section B), aesthetics (the Section C), information (Section D), and perceived subjective impact (Section E). The BRCApp information and contents, as planned, turned out to be the main means to improve end-user's eBrave study outcomes, such as the monitoring and improvement of weight and abdominal circumference, following diets and physical exercises suggestions. Indeed, the uMARS information section obtained the highest scores, both for medians and correlations with Days of Activity, and, in this particular case, represented a good starting point to obtain a good final outcomes (Table 6)

Finally, the correlation between the app's days of use and the section's uMARS score was used to evaluate the effective influence of a real app use (not just a first interaction) on the obtained usability scores. This is important to objectively evaluate the results, without taking conclusions that are decoupled from the effective use of the app. Indeed, this consideration is highlighted by the results in the Paragraph 3.3, showing that the correlations in general were statistically significant after at least seven days of use (TH=7). This matches the idea that the perceived usability is effectively influenced by a real app usage.

4.2. Limitations

While the current research has provided a valid solution to develop mHealth app-based RWD platform and validate it from the end-user's point of view, through a usability evaluation in a real-world setting, three main limitations emerged along this journey, spread on the three levels on which this thesis was divided:

- **Literature Research Limitation (Chapter 1):** a non-systematic review to answer to the research questions 1 and 2 was conducted. This type of scoping review was enough for the thesis purpose. However, it lacked a rigorous systematic process of paper selection, that could lead to a lack of reproducibility. In any case, the extracted definitions, concepts, tools and frameworks, demonstrated to be the most used in literature, and they were reviewed under both a professional and technical point of view.
- **Development and Implementation Limitation (Chapter 2):** when the second version of the RWD LifeCharger SynCare platform was developed, to share personal RWD to the Data Analytics module, a pseudo-anonymization process based upon RSA keys was adopted. Anyway, this could not be the best solution, because part of not sensitive data are stored as decrypted. As Chapter 1 recommended, one method to analyse and operate on complete encrypted data could be homomorphic-based cryptography. This could lead to manage RWD without working directly with decrypted data, but it would involve higher development and computational efforts.
- **Usability Evaluation limitation (Chapter 3):** the usability BRCApp evaluation during the eBrave study did not start at the very beginning (June 2024), but few months after the starting point (February 2025). Thus, it could be that some BRCApp's users filled in the uMARS questionnaire after several months of app use, differently from app users that filled it after just seven days of use. This could lead to some bias and differences in the app evaluation (for example, one prolonged use could bring to more engagement than seven days of use, or even that the users already left the study, before the evaluation).

4.3. Future Works

The presented mHealth-based LifeCharger's platform has the potentiality to be improved, optimizing the existent cybersecurity infrastructure and integrating artificial intelligence (AI).

As described in paragraph 2.3.4, the mobile app suffers the limitation of having a slow decrypting time of data when the app is opened or refreshed. To solve this problem, we are currently working on three different solutions. Firstly, adding the implicated data to be decrypted to a local database, thus, avoiding the decrypting each time. The second optimization involves the decoupling of the different UI views loading. In fact, loading in parallel the different batch of data that are needed to construct the different app views, drastically reduce the loading time, reducing the computational cost on the main thread, that risks to blocks the app, as well. The last implementation that can bring to a significant reduction of loading time could be limiting the data queries to a date more recent than thirty days ago, leaving to the user the possibility to explore the calendar until maximum of thirty days ago.

Beyond the UX app optimization, the version 2.0 has laid the foundation to upgrade the security, sending data in an anonymous way, replacing the end-to-end channel between a user and a professional of the version 1.0 with a one professional-to many users' approach. In this scenario, the homomorphic cryptography could be applied to the batch of anonymous user's data sent to the Data Analytics module for the analysis purpose. Thus, the Data Analytics Module could operate and make calculation on data without seeing any decrypted meta-data.

Finally, artificial intelligence (AI) integration could be the future of Data Analytics module. Predictions, reports, supervision, and monitoring, are operations that can be support by novel large language models (LLM). LLM, in a conversational or API methods, could lead the professionals to optimize their work experience and support them for making decisions. In addition, reporting and feedback to the users based on their self-reported data could be enriched automatically by applying LLM methods to their data. However, implementing AI will encounter new normative, such as the European AI Act, that will be fully applicable on August 2026 (https://digital-strategy.ec.europa.eu/en/policies/regulatory-framework-ai#1720699867912-1), and the Ethics Guidelines for Trustworthy AI, that put forward a set of 7 key requirements that AI systems should meet in order to be deemed trustworthy (https://digital-strategy.ec.europa.eu/en/library/ethics-guidelines-trustworthy-ai).

An AI integration example applicable to the e-Brave study could be the implementation of an intelligent recipe suggestion system that depends on users' diet and behaviour during their journey. Indeed, having the possibility to acquire questionnaires regarding their dietary habits (er-MEDAS), the SynCare Data Analytics module could evaluate users' answers, fetch the different uploaded recipes, and propose to users the best recipe contents based on their interests. However, this simple

solution requires, beyond engineering evaluations (“what AI models to choose?”, “Should we use existing commercial models or implement our own?”, “Open-source on a local machine, or via API?”, etc.), also a risk evaluation during the design phase, due to the upcoming cited AI Act.

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A Appendix A

The following tables are cited in Chapter 1:

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Table A 1: RWD definitions and sources resulting from the non-systematic literature review

Reference	RWD Definitions	RWD sources
Zhang, J., et al., Best practices in the real-world data life cycle. PLOS Digit Health, 2022. 1(1): p. e0000003. [2]	Observational data generated during routinely healthcare provision, excluding data generated experimentally (for example, while conducting a clinical trial)	Electronic Health Records; patient or diseases registries; genomics from biobanks; patient-generated data from mobile apps (from PROMS) and wearables; claims and reimbursements; observational databases
Gilbert, S., et al., Continuous Improvement of Digital Health Applications Linked to Real-World Performance Monitoring: Safe Moving Targets? Mayo Clinic Proceedings: Digital Health, 2023. 1(3): p. 276-287. [20]		Electronic Health records (such as demographic characteristics, anamnesis, family history, all clinical test results, and medication data), health insurance claims, user surveys, patient surveys, wearable and digital health application (DHA)-derived data (from DHAs other than the DHA under surveillance), environmental data, user location data, social media analytics, and web and literature data, feedback from individuals in the target populations (often but not always patients) and feedback from individuals in the user population

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Cho, S., et al., Factors Affecting the Quality of Person-Generated Wearable Device Data and Associated Challenges: Rapid Systematic Review. JMIR Mhealth Uhealth, 2021. 9(3): p. e20738 [85]		Patient-generated health data (PGHD): data collected passively through sensors, such as step counters, heart rate and sleep quality; data entered directly by the user, such as diet, stress levels, and quality of life; social or financial info that is not specifically health related but potentially could provide health-related insights; patient-generated data by wearables
Pulini, A.A., et al., Impact of Real-World Data on Market Authorization, Reimbursement Decision & Price Negotiation. Ther Innov Regul Sci, 2021. 55(1): p. 228-238. [15]	International Society for Pharmacoeconomics and outcomes research (ISPOR): RWD can be considered as everything that goes beyond what is normally collected in traditional phase III clinical trial programs and is used for clinical, coverage, and payment decision making. In 2017, at least 38 definitions were identified and classified into 4 categories: 1) non-RCT settings (all health data except those collected in the setting of a convectional phase III RCT setting); 2) non-interventional/non-controlled	ISPOR identified 6 sources divided by 3 types: 1) institutional data (clinical and administrative data); 2) patient-generated data. As source, mobile health devices and software applications and social media have been cited for their relative usefulness for effectiveness assessment and to collect data regarding adherence to treatment and symptom occurrence in real life scenarios.; 3) emergent data, or big data, in general cannot "automatically" be classified as RWD that once analyzed generate RWE.

	setting (data collected without interference with treatment assignment, and/or patient monitoring/follow-up, and/or selection of study population); 3) non-experimental setting (the investigator has no control over any of the conditions and no de novo data collection occurs on the basis of a pre-established study protocol); 4) others (none of the aforementioned). Large inclusive IMI-GetReal consortium definition: RWD are an umbrella term for a variety of data types concerning the effects of health interventions that are not collected in the context of highly controlled, idealized conditions of RCTs (close to ISPQR definition focused on purpose/aim of RWD = "decision-making"). RWD can concern NOT ONLY "real-word" monitoring of DRUGS, but all health products (including medical devices), and more generally all treatments and care practices..	

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Wehrle, K., et al., Implementation of a data control framework to ensure confidentiality, integrity, and availability of high-quality real-world data (RWD) in the NeuroTransData (NTD) registry. JAMIA Open, 2022. 5(1): p. ooac017. [12]	RWD are data that reflect actual healthcare encounters in daily practice	Laboratory results and patient-reported outcomes collected using tablets and smartphones

Bourke, A., et al., Incorporating patient generated health data into pharmacoepidemiological research. Pharmacoepidemiol Drug Saf, 2020. 29(12): p. 1540-1549. [3]	RAND Europe definition: "an umbrella term for different types of health care data that are not collected in conventional RCTs. RWD in the health care sector come from various sources and include patient data, data from clinicians, hospital data, data from payers, and social data". The U.S. Food and Drug Administration definition: "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources".	Patient-generated health data (PGHD) as patient-centric insight not readily available in routine healthcare datasets: 1) demographics (educational level; financial situation; living conditions; family health history), collected actively via self-report questionnaires and passively with geolocation (infer socio-economic status via linkage to "national" style database); 2) patient experience and opinion (drug side effects; symptoms; treatment satisfaction; perceived barriers to adherence), collected actively with questionnaire eliciting information on pain/symptom or other details, and passively reusing of social media data; 3) behavior and exposure (diet; physical activity and movement; treatment adherence; environmental exposures e.g. climate, air, pollution), collected actively by questionnaires or e-diary to monitor dietary intake, exercise etc..., and passively by

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		accelerometers to measure physical activity, GPS sensor in smartphone linked to environmental monitors; ingestible sensors to measure medication adherence; 4) physiological measurements (blood pressure, blood chemistry, weight, physical assessment) collected actively by home-monitoring (BP, glucose) and connected devices, (weight) and passively using implantable and wearable devices, e.g. sensor in brace after knee replacement to measure joint flexibility, \or smartwatch to measure heart rate

Choo, H., et al., Influenza Screening via Deep Learning Using a Combination of Epidemiological and Patient-Generated Health Data: Development and Validation Study. J Med Internet Res, 2020. 22(10): p. e21369. [86]		Office of the National Coordinator for Health information Technology Patient-generated health data (PGHD) definition: health-related data, treatment history, lifestyle choices, and other information - created, recorded, gathered, or inferred by or from patients or their designees (i.e. care partners or those who assist them) to help address a health concern

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Wise, J., et al., The positive impacts of Real- World Data on the challenges facing the evolution of biopharma. 2018. [87]	RWD definition from the Duke-margolis Center: data relating to patient health status and/or delivery of health care routinely collected from a variety of sources. This definition does not preclude the incorporation of routinely collected data in traditional randomized controlled trials.	Electronic health records (EHRs), administrative and claims data captured directly during an observational study, from sources patient-generated information outside clinical settings (e.g., in-home monitoring devices and wearable technologies), and in patient registries, contextual metrics such as environmental exposures and socioeconomic indicators. Any sources that formalize information related to medicine adherence and experience (hospital-level diagnostic notes, data from IoT-enabled medical equipment, smartphones, and wearables collecting vital and environmental info).

Khosla, S., et al., The Alignment of Real-World Evidence and Digital Health: Realising the Opportunity. Ther Innov Regul Sci, 2021. 55(4): p. 889-898. [4]	Real world data (RWD): longitudinal patient-level data captured in the routine management of patients (for care, cost management or public health) which can be repurposed to study the impact of healthcare interventions, that can be seen as "Digital health data: the (passive or active) collection of health data via a digital tool, device, wearable or app", which analysis derives the digital health evidence	Health apps, digital devices (wearables)

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Liu, F. and D. Panagiotakos, Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol, 2022. 22(1): p. 287. [16]	Definition by US FDA: RWD in the medical and healthcare field are related to patient health status and/or the delivery of health care routinely collected from a variety of sources.	1) EHRs: collected as part of routine care across clinics, hospitals, and healthcare institutions, 2) registry data: product registries including patients who have been exposed to a biopharmaceutical product or a medical device, health registries that consists of patients who have had a common procedure or hospitalization, and disease registries containing info 3) claims data: data generated during processing healthcare claims in health insurance plans of from practice management systems 4) patient-report outcome (PRO) data: reported directly by patients on their health status, and 5) collected from wearables: continuous stream of data.

Klonoff, D.C., F. King, and D. Kerr, New Opportunities for Digital Health to Thrive. Diabetes Science and Technology, 2019. 13(2): p. 4. [13]	RWD are data obtained from outside of conventional clinical trials	Electronic health records (EHRs), insurance claims, pharmacy records, patient registries, and mobile apps.
Milne-Ives, M., M.H. van Velthoven, and E. Meinert, Mobile apps for real-world evidence in health care. J Am Med Inform Assoc, 2020. 27(6): p. 976-980. [17]	The FDA defined RWD as: data… from electronic health records (EHRs), claims and billing data, … product and disease registries, patient-generated data … and … other sources that can inform on health status, such as mobile devices.	Electronic health records (EHRs), claims and billing data, … product and disease registries, patient-generated data … and … other sources that can inform on health status, such as mobile devices (active collection and passive sensing and task-based data to measure daily activity and mental state, physiological status, and performance in physical or cognitive tasks)

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King, D.R., et al., Methods for Navigating the Mobile Mental Health App Landscape for Clinical Use. Curr Treat Options Psychiatry, 2023: p. 1-15. [14]	RWD is data relating to patient health status or care delivery.	
op den Akker, H., M. Cabrita, and A. Pnevmatikakis, Digital Therapeutics: Virtual Coaching Powered by Artificial Intelligence on Real-World Data. Frontiers in Computer Science, 2021. 3. [18]	The Food and Drug Administration (FDA) defines Real-World Data (RWD) as "data related to patient health status and/or the delivery of health care routinely collected from Electronic Health Records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices" (US Food and Drug Administration, 2017)	1) Objective RWD: measurements from mobile devices, manufactured either for medical or wellness purposes (quality only depends on the devices' measurement accuracy), and 2) subjective RWD: patient-generated reports (accuracy depends on the patients' understanding of the assessment, on their objectiveness and on their accuracy in data entry)

Zou, K.H. and M.L. Berger, Real-World Data and Real-World Evidence in Healthcare in the United States and Europe Union. bioengineering, 2024. 11(784). [19]	United States (US) Food and Drugs Administration (FDA) definition: "Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Examples of RWD include data derived from electronic health records, medical claims data, data from product or disease registries, and the data gathered from other sources (such as digital health technologies) that can provide information regarding patient health status"	Structured data: diagnosis codes, procedure codes, prescriptions written, dates of eligibility, dates of service, and many others. Other types derived from 21st Century Cures Act, when RWE was defined by the US Congress: electronic health records (EHRs), 'omics data, specimens, voice recordings, images, texts, and sensor data from wearable devices and health apps

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Khatiwada, P., et al., Patient-Generated Health Data (PGHD): Understanding, Requirements, Challenges, and Existing Techniques for Data Security and Privacy. Personalized Medicine, 2024. 14(282). [23]		Personal-Generated Health Data (PGHD): health-related data created, recorded, or gathered by or from patients (or family members or other caregivers) to address health concern. PGHD TYPES and SOURCES: 1) Wearable Data: fitness trackers (eg. Fitbit, Garmin, Apple Watch), health specific wearables (eg. continuous glucose monitors), smart clothing (garments with embedded sensors); 2) Self-Report Outcomes: health diaries (daily or weekly record of symptoms, diet, medication intake, etc…), survey and questionnaires (patient-reported outcomes measurement information system, called PROMIS), mobile apps (health and wellness app that allow users to input data related to nutrition, mood, menstral cycles, pain levels, etc…); 3) Home Monitoring Devices: blood pressure monitor at home, glucose meters, pulse oximeters, electronic scales to monitor weigth, smart

		thermometers (track and record temperature readings); 4) Connected Medical Devices: smart inhalers, digital pills with edible sensors, implanted devices; 5) Social & Lifestyle Data: dietary intake (apps or platform where users input their daily meals and snacks), exercise & physical activity logs (manually record workouts or sport activities outside wearables), mental well-being apps (mood trackers or meditation apps); 6) Environmental Data: air quality monitors and home sensor (mold, pollen, etc…); 7) Social Network and Media Data: post and interactions, activity patters (eg. time spent on social and activity timing), connection maps, communication analysis.

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Table A 2: Different definitions of RWD life cycle and description

Reference	RWD Cycle Definition/Description
Zhang, J., et al., Best practices in the real-world data life cycle. PLOS Digit Health, 2022. 1(1): p. e0000003. [2]	1) Data life cycle that carries data from disparate sources through to final application. 2) Data life cycle is a series of necessary or recommended steps that produce RWD usable for analysis, from raw data generated by clinical encounters or operational workflows 3) The authors summarize a RWD life cycle as a process that includes acquisition, aggregation and enrichment, maintenance, and usage of data. They divided RWD life cycle into 4 stages: 1) acquisition; 2) aggregation/enrichment; 3) maintenance; 4) usage.
Liaw, S.T., et al., Quality assessment of real-world data repositories across the data life cycle: A literature review. J Am Med Inform Assoc, 2021. 28(7): p. 1591-1599. [24]	Data creation and collection to the extract, transform, and load process; data processing and annotation with metadata; and curation, visualization, and sharing

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Liu, F. and D. Panagiotakos, Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol, 2022. 22(1): p. 287. [16]	They described the cycle through the actors actions: 1) individuals who supply the data, 2) those who collect and manage the data, 3) data curators who design studies and analyze the data, and 4) decision and policy makers
Khosla, S., et al., The Alignment of Real-World Evidence and Digital Health: Realising the Opportunity. Ther Innov Regul Sci, 2021. 55(4): p. 889-898. [4]	Called RWE value chain: 1) patient as our source of information, from whom we collect data. 2) Data are then stored and transmitted so 3) it can be aggregated with data from other patients. Finally, 4) data are analyzed to generate RWE for final use by stakeholders.

Table A 2 - Continued on next page

Table A 3: RWD features and factors affecting their quality

Reference	Features of RWD for quality	Factors affecting data quality
Liaw, S.T., et al., Quality assessment of real-world data repositories across the data life cycle: A literature review. J Am Med Inform Assoc, 2021. 28(7): p. 1591-1599. [24]	1. INTRINSIC FEATURES: conformance, completeness, and plausibility 2. CONTEXTUAL Data Quality (DQ) CATEGORY: data organization (timeliness, trustworthiness, relevance, accessibility, reusability, governance) 3. TECHNICAL DQ: traceability and interoperability.	

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Cho, S., et al., Factors Affecting the Quality of Person-Generated Wearable Device Data and Associated Challenges: Rapid Systematic Review. JMIR Mhealth Uhealth, 2021. 9(3): p. e20738. [85]	1) completeness, 2) correctness, and 3) heterogeneity: heterogeneity of data exists at three levels: 1) single-person data (a data set generated by a single person), 2) single-device data (data set generated by multiple people who use the same brand, model, and version of device; e.g., a data set consisting of data generated from Fitbit Charge HR), and 3) multidevice data (a data set generated by multiple people who use diverse brands, models, and versions of devices, eg, data set consisting of data generated from Fitbit Charge HR, Fitbit Alta HR, Withings Steel HR Sport, Apple Watch Series 3, etc).	1) Device- and Technical-Related Factors: issues related to hardware (sensor malfunction, the quality of sensors, and sensor degradation over time, software (major issue is that consumer wearables use proprietary algorithms for their devices), and network and Bluetooth (Lack of wireless signals or lost satellite connection) 2) User-Related Factors: Missing data that occur from nonwear is a major limitation to the accuracy of estimate 3) Data Governance-Related Factors: Lack of standardization can cause significant heterogeneity across data from different device brands (eg, Fitbit vs Garmin) or different models within the same brand (eg, Fitbit Charge 3 and Fitbit Inspire) and more broadly across individuals and different clinical centers.

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Wehrle, K., et al., Implementation of a data control framework to ensure confidentiality, integrity, and availability of high-quality real-world data (RWD) in the NeuroTransData (NTD) registry. JAMIA Open, 2022. 5(1): p. ooac017. [12]	1) stored securely ("confidentiality"), 2) cannot be accidentally modified in unpredicted ways ("integrity") and 3) is ready for analyses in a timely manner ("availability")	Inconsistencies, gaps, or erroneous data

Bourke, A., et al., Incorporating patient generated health data into pharmacoepidemiological research. Pharmacoepidemiol Drug Saf, 2020. 29(12): p. 1540-1549. [3]	1) reliability/accuracy 2) completeness 3) timeliness	1) When considering specific methods to collect physiological Patient-generated health data (PGHD), such as self-measured blood pressure, reliability may be poor compared to clinician-led collection. By contrast, collecting PGHD on behavior, such as physical activity, wearable devices can improve accuracy when compared to questionnaires and can decrease recall bias and underreporting. 2) unstructured data. 3) Temporally dense PGHD data: Many digital devices can generate temporally dense data, such as continuous recording of heart rates or blood pressures 4) Selection bias: if patient characteristics that underlie the ability to create PGHD (eg ownership of certain digital devices) are associated with both exposure and outcome of interest. Careful examination of differences in characteristics of participating vs. excluded patients is recommended, at least for a random sample of individuals; 5) missing data: PGHD

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		may be incomplete for practical reasons such as battery dependency, Wi-Fi reach, devices taken off for bathing, as well as patients failing to record things.
Liu, F. and D. Panagiotakos, Real-world data: a brief review of the methods, applications, challenges and opportunities. BMC Med Res Methodol, 2022. 22(1): p. 287. [16]		1) RWD are often used for other purposes than what they are originally collected, 2) RWD are messy, heterogeneous, and subject to various measurement errors, all of which contribute to the lower quality of RWD compared to data from controlled trials.

Damen, D.J., et al., Patients Managing Their Medical Data in Personal Electronic Health Records: Scoping Review. J Med Internet Res, 2022. 24(12): p. e37783. [30]		1) patient-related: 6 themes that determined whether patients entered, updated, or modified their core medical data: patient demographics; digital and health literacy; concerns related to the accuracy, validity, privacy, and confidentiality of recorded data; misconceptions about the applicability; and usefulness of patient-entered data 2) healthcare provider-related: Encouraged use by health care providers and the patient-clinician relationship are identified as the 2 important factors determining whether patients actively manage their core medical data. 3) system-related: patient satisfaction with the system used to collect and maintain their core medical data is an important factor that stimulates active data management. 6 main themes emerged from the data extraction that concerned system-related facilitators and barriers affecting patients' satisfaction with the tools used to record their medical core data: the level of customization, usability of the system or

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		tool, guided versus free data entry, presence of visual cues, reminders, and fee-free access to the system/tool

Zou, K.H. and M.L. Berger, Real-World Data and Real-World Evidence in Healthcare in the United States and Europe Union. bioengineering, 2024. 11(784). [19]	From FAIR principles: findability, accessibility, interoperability, and reusability. Other cited features: data discoverability and linkage, security and privacy 5 dimensions from author ATRAcTR (meaning: Authentic Transparent Relevant Accurat Track-Record) framework: 1) authenticity (provencance documentation, ability to verify source, changes in data collection over time, de-identification and privacy protection); 2) transparency (data extraction, transformation and loading, handling of incorrect or missing data, linkage, handling of free-text and changed in coding conventions, data latency and refresh rate, inclusion of synthetic data); 3) relevancy (sample size of interest, representiveness, length of follow-up, demographic characteristics); 4) accuracy (data integrity-quality checks, including conformance, plausibility, completeness,	Technical challenges affecting system interoperability and data privacy: 1) non-unique patient identification numbers 2) used semantics 3) different common data models (CMDs) used

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	uniqueness of records, continuity of data collection, ability to audit key variables); 5) track record (historical performance of data set in creating credible RWE	

Liaw, S.T., et al., Quality assessment of real-world data repositories across the data life cycle: A literature review. J Am Med Inform Assoc, 2021. 28(7): p. 1591-1599. [24]		Challenges associated with the use and implementation of Patient-Generated Health Data (PGHD): 1) Data Accuracy affected by 1. Variable quality: devices and apps vary in their accuracy and reliability (eg. one fitness tracker measures steps differenty from another), and 2. Patient input errors: manual data entries can be prone to inaccuracies or inconsistencies. 2) Integration with Clinical Settings problems due to 1. Interoperability Issues: clinical systems as electronic health records (EHRs) might not easily ingrate with PGHD sources; 2. Data Overload: volume of PGHD can be overwhelming. 3) Patient Adherence can affect 1. Consistency: patients might not consistently use wearables or input data in apps (gaps in data); and can be due to 2. Motivation: maintaining motivation to regularly input data or use health-tracking tools (especially if patients do not see immediate benefits).

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		4) Data Interpretations problems due to 1. Context Lacking (PGHD can be misleading); and 2. Healthcare Provider Training: not all providers my be trained or feel comfortable interpreting PGHD (understanding of diverse sources) 5) Standardization problems due to 1. Varied Data Format from different sources (aggregation and analysis problems); 2. Lack of Industry Standards: limited clinical utilty. 6) Patient Education & Engament can affect the 1. Effective Use: patients need to be edutated (how to use the apps or devices to ensure that data collected is of value); 2. Understanding Data: patients can misinterpret their data, leading to unnecessarhy ansiety or incorrect self diagnosis). 7) Clinical Relevance affected by 1. Data Not Always Clinically Useful: not all PGHD can be releveant for clinical decisions; 2. Potetial to Overwhel: excessive data can lead to “alert fatigue”.

		8) Economic & Access Issues due to 1. Cost Barriers: not all patients can afford smart wearables or devices (disparities); 2. Technological Literacy issues: not everyone is tech -savvy (challenging in navigating apps) 9) Regulatory & Ethical Concers due to 1. Liability Issues: PGHD indicates a health issue but is not acted on; 2. Consent & Ownership: clear guidelines on who owns PGHD and how it can be used.

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Table A 4: Different tools/framework descriptions for managing and assessment of RWD quality

Reference	RWD quality framework description
Wehrle, K., et al., Implementation of a data control framework to ensure confidentiality, integrity, and availability of high-quality real-world data (RWD) in the NeuroTransData (NTD) registry. JAMIA Open, 2022. 5(1): p. ooac017. [12]	A framework based on COBIT framework and ISO 27001 standard, and it relies on 5 elements: 1) access and change management: roles and responsibilities for the data journey are defined and an inventory of involved staff and systems exists. Based on these roles, access rights to the individual systems are provided. Up-to-date lists of active users per systems are reviewed regularly. Changes are made following an Agile process. 2) Business continuity management. 3) Data operations regarding data input: control audits of source data monitoring within the annual recertification for the ISO 9001 certification of NTD offices; automatic quality assurance queries are in place for all data entries, to identify inconsistencies, gaps, or erroneous data. Missing data trigger notifications in a weekly report shown to the doctor in the registry web-application dashboard in context specific form (e.g., the doctors can see all alerts that correspond to a given patient) to support data completeness. 4) Transfer of patient data: each step of the transfer of data from NTD to the DPS follows a regulated and fully documented process. Once every quarter of the year, the registry data are extracted by NTD as a set of flat files from a database backup. A control is implemented to ensure completeness and accuracy of the data export. Controls for data processing at the DPS: after downloading the flat files generated by NTD, checks for accuracy and completeness are performed by the DPS based on the checksum string of the downloaded data package. All file sizes are also compared to the sizes of the last quarter using an

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	automated Rscript, since the file size should increase steadily. The reconciliation results are then stored. If all data import controls have been passed, the flat files are imported by a bulk insert statement as part of a set of SQL scripts to a dedicated database management system, whereby each year's data is stored in a separated database. The bulk insert statement is stored on a version-controlled repository and manually executed. A further completeness check is performed after the data import, whereby the export summary report provided by NTD is compared to the imported data. The data preparation process now starts via a set of SQL scripts performing data cleaning and transformation. Duplicate records are identified and removed by comparing all attributes. For all data tables, additional data cleaning steps are performed based on plausibility checks: in these checks, records are removed based on either missing information or implausible dates (eg, diagnosis dates in the future). Plausibility of results: Once the process is finished, an analysis of change (AoC) is being performed on the original and the cleaned data to compare the cleaning process for each quarter and the development of the main modules, ie, number of patients, therapies, events, relapses, and visits. In case these changes are not plausible, a cross check with NTD is performed using the issue-tracking system (eg, an office may have conducted an enrollment initiative). 5) Controls for completeness and accuracy: - Implementation of standardized user interfaces and masks for data entry and data definitions to avoid inconsistencies during entry. - IT support provided for all users and error management is in place. In an NTD-internal online forum, questions on functionalities are answered and detailed information on specific workflows of DESTINYVR are documented. - The version history for the registry database with information about added or changed features and solved bugs is also available in the

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	forum. - Processes are described and available for all users and regular training sessions are provided. - Availability of resources for data management and security is checked regularly. - A joint registry steering committee meets to check and discuss data quality issues.

Liaw, S.T., et al., Quality assessment of real-world data repositories across the data life cycle: A literature review. J Am Med Inform Assoc, 2021. 28(7): p. 1591-1599. [24]	Six proposed frameworks/tools: 1) Harmonized intrinsic DQ framework (HIDQF): In 2016, an international DQ research collaboration reviewed the literature and developed and published a harmonized framework. This framework defined 3 DQ categories—conformance, completeness, and plausibility—and 2 DQ assessment contexts—verification and validation. Conformance and plausibility categories are further divided into subcategories and terminology to assess the intrinsic quality of a dataset (Paper: A harmonized data quality assessment terminology and framework for the secondary use of electronic health record data). 2) The Quality Knowledge Repository was developed to store DQ Concepts and their methods of computation across information quality (IQ) domains with relationships across domains determined by a DQ meta-model; this knowledge repository has been leveraged into a service-oriented architecture to perform as a scalable and reproducible framework for DQ assessments of disparate data sources. 3) Web-based tools such as the TAQIH (tabular DQ assessment and improvement for health) have been developed to conduct exploratory data analyses to improve completeness, accuracy, redundancy, and readability. 4) ACHILLES (Automated Characterization of Health Information at Large-scale Longitudinal Evidence Systems) tool was developed and maintained by the OHDSI collaborative to conduct DQ checks on databases that are based on or mapped to the Observational Medical Outcomes Partnership Common Data Model (CDM). Well tested, including a published application to 24 large healthcare datasets across 7 different organizations in America, Europe, and Asia. This CDM-enabled rapid comparisons of the

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	DQ of multiple international datasets reduced the data model variations and increased the robustness and generalizability of the methods and outputs. These findings also highlighted the importance of interoperability, a FAIR guiding principle, as a core component of DQ assessment of RWD repositories that integrate data from multiple EHRs and health information systems; 5) The OHDSI Data Quality Dashboard (https://ohdsi.github.io/ DataQualityDashboard/) has been developed based on the HIDQF and Achilles. It is a potential mechanism to standardize DQ assessment of RWD within a CDM; 6) FAIR principles/Three-point FAIRification Framework provides practical "how to" guidance to stakeholders seeking to go FAIR (https://www.go-fair.org/how-to-go-fair/)

Zou, K.H. and M.L. Berger, Real-World Data and Real-World Evidence in Healthcare in the United States and Europe Union. bioengineering, 2024. 11(784). [19]	1) FDA's (US) "Advancing Real-World Evidence Program" that follows various regulatory frameworks; 2) The European Health Data Space (EHDS) that aims to foster cross-border data exchanges and transfers to support healthcare delivery, research, and innovation. 3) The European Medicines Agency (EMA) proposed a reflection paper that follows the principles of transparency, reliability, extensiveness, coherence, and timeliness; 4) The authors proposed the ATRAcTR (meaning: Authentic Transparent Relevant Accuract Track-Record) framework that uses criteria consistent with frameworks promoted by FDA and EMA 5) The Health Insurance Portability And Accountability Act (HIPAA) to address privacy concerns in US 6) The General Data Protection Regulation (GDPR) to address privacy concerns in EU 7) The California Consumer Privacy Act (CCPA) to enhance consumer privacy rights and imposes obligations on business regarding the collection, use, and sale of personal information in US

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Table A 5: different evaluations of mHealth App Quality, with related context and features

Reference	mHealth App Quality Evaluation Context	Features for quality
Gilbert, S., et al., Continuous Improvement of Digital Health Applications Linked to Real-World Performance Monitoring: Safe Moving Targets? Mayo Clinic Proceedings: Digital Health, 2023. 1(3): p. 276-287. [20]	PRE/POST-Market Surveillance	1) Real-World Data for evaluating quality of an App 2) Usability standards for reaching quality

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Essén, A., et al., Health app policy: international comparison of nine countries' approaches. npj Digital Medicine, 2022. 5(1). [21]	Focus on different countries evaluating the mHealth Apps	1) Dependent on the country framework 2) Levine et al subdivided by 5 categories the evaluation of the Apps: 1) transparency: info about app to end-user, basis for content; 2) health content: evidence basis appropriateness of measurement and interpretation; 3) technical content: software performance interoperability/bandwidth requirements/application size; 4) security/privacy: authentication/anonymization, protection against theft, viruses/signaling of breaches/data sharing/maintenance; 5) usability: ease of installation and user/tailoring/multiple languages

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Portz, J.D., et al., "I Like the Idea of It...But Probably Wouldn't Use It" - Health Care Provider Perspectives on Heart Failure mHealth: Qualitative Study. JMIR Cardio, 2020. 4(1): p. e18101. [31]	They found out 5 themes (after semi-interview analysis) that can be used to evaluate an App, from the professionals/healthcare providers point of view.	1) Bio-Psychosocial-Spiritual Remote Monitoring: psychosocial assessments and questions about practical help, while less interesting to clinical providers, were recognized to get a more well-rounded picture of patients with complex chronic illness 2) Sensor Technologies and Potential of Real-Time Data: sensor technology such as weight tracking, home blood pressure monitoring, and physical activity monitoring and its utility in minimizing patient-driven data collection 3) Interoperability for a Personalized Experience: potential to sync patient-generated data with the electronic health record and patient portal, and interface with other apps that provide psychosocial support, reporting it to be useful to sync with other commonly used apps (e.g., mindfulness apps, music apps, Google calendars, and shared-list apps 4) Tailored Assessment and Sharing of Data: caregivers having access to patient data would be helpful (privacy/security problems as consequence) 5) Usefulness of Patient-Reported Outcomes in Practice: providers almost unanimously preferred graphs showing trends in HF symptoms and physiologic measures. Many providers were concerned with facilitating data collection in a patient-centered, noninvasive way that does not collect more data than used.

Milne-Ives, M., M.H. van Velthoven, and E. Meinert, Mobile apps for real-world evidence in health care. J Am Med Inform Assoc, 2020. 27(6): p. 976-980. [17]	Quality intended for Mobile Health App to Collect RWD	1) Purpose for which the App is designed: many health apps are not designed for research, which can affect data quality—a primary concern of patient-generated data 2) Data quality: lack of validated and reliable measures through mobile health apps 3) Privacy and security: lack of patient trust and willingness to share data 4) Methods of analysis: data are overwhelming and difficult to use in research, in clinics, and by patients 5) Standardization and integration of data: real-world data cannot all be combined and assessed as a whole 6) Health equity: use of mobile health apps is weighted toward younger, more educated, and more e-health–literate people 7) Regulation of mobile health apps: little regulation of mobile health apps that are not classified as "medical devices" with potential risk to public health; 8) Long-term use: loss of motivation to keep using a mobile health app 9) Integration into established routines: lack of understanding of how new technology can best fit into existing workflows

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Damen, D.J., et al., Patients Managing Their Medical Data in Personal Electronic Health Records: Scoping Review. J Med Internet Res, 2022. 24(12): p. e37783. [30]	Quality intended for a generic system that is used by patients to manage their data	1) Usability: patients' (continued) use of their electronic patient portal to generate and update their core data depends on the perceived complexity and thus the usability of the system or tools used 2) Guided Data Entry: unless patients are being asked to enter information about simple diagnoses or prescriptions, systems should use guided entry of data elements 3) Visual Cues: implementing visual feedback facilitates data entry by patients and patients' satisfaction with using the system. For instance, providing medication pictures alongside a selected medication assists patients' medication reconciliation. 4) Reminders: if reminded to do so, patients are more likely to use the portal before and after their outpatient visits 5) Providing applications without charge that can be downloaded by patients as well as by a more general group of users stimulates the accumulation of patient-generated core medical data

King, D.R., et al., Methods for Navigating the Mobile Mental Health App Landscape for Clinical Use. Curr Treat Options Psychiatry, 2023: p. 1-15. [14]	Mental health and wellness apps on the market	1) The paper authors propose to evaluate the app following 4 factors: 1. clinical and privacy considerations, 2 ease of use, 3. diversity of perspective in creation of the model, and 4. adoption of the model 2) Quality evaluation based on 3 levels: 1 US Government: broadest level at which app evaluation must happen is at the US governmental level; 2. Health system: At a healthcare system level, leaderships are seeking ways to systematically incorporate mobile app evaluation and integration into clinical psychiatric. In researching current practices, we see the emergence of two models within healthcare systems: the creation of “digital clinics,” and the use of “digital care navigators.” practice; 3. Individual clinician-patient: at the most basic level, there is a need on an individual level for clinicians and patients to independently evaluate apps" 3) Informed consent: The American Psychiatric Association (APA) ethics committee recommends that healthcare professionals engage in an informed consent process stating the potential risks inherent to using an app, including a loss of personal privacy and more 4) reimbursement: reimbursement for a clinician in the use of mental health apps in clinical care is inconsistent with respect to current practice management and delivery systems models. For instance, 2023 Remote Therapeutic Monitoring (RTM) offers a Current Procedural Terminology (CPT) code of 98,978. This code allows a practitioner to bill for the use of a Cognitive Behavioral Therapy device.

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Table A 6: different tools/frameworks for of mHealth app quality

Reference	mHealth App Quality Evaluation Context	Tools/frameworks for quality assessment
Gilbert, S., et al., Continuous Improvement of Digital Health Applications Linked to Real-World Performance Monitoring: Safe Moving Targets? Mayo Clinic Proceedings: Digital Health, 2023. 1(3): p. 276-287. [20]	PRE/POST-Market Surveillance	1) A/B-test, which can compare 2 system features or PROMS; 2) The System Usability Scale can be used for the assessment of usability, and 3) the Mobile App Rating Scale can be used for systematized assessment of a mobile application's quality, including in comparison with the state of the art

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Essén, A., et al., Health app policy: international comparison of nine countries' approaches. npj Digital Medicine, 2022. 5(1). [21]	Focus on different countries evaluating the mHealth Apps	1) Germany: there is DIGA that implements FAST TRACK framework. Apps approved for use and reimbursement are available in a central directory of digital health App 2) Belgium: there is mHealthBelgium validation pyramid framework, that evaluates Apps on three levels, each consisting of criteria related to regulatory issues (level 1), safe communication and privacy (level 2), and to financing and reimbursement (level 3). 3) England: emerging frame under development: Digital Technology Assessment Criteria (DTAC) https://www.nhsx. nhs.uk/key-tools-and-info/ digital-technology- assessment-criteria-dtac/ (n. d.)). 4) Levine et al divided the tools depending on the evaluation category. 1. for transparency (intended use, medical trials to evaluate app, GDPR compliance): the emerging ISO standard, suggests users should consent to advertisements and use of data and requires the description of the app (in e.g., an App store) to be 'accurate and clear '(https://www.iso.org/standard/78182.html (2021)); 2. for health content (evidence supporting the intended use): the emerging ISO standard refers to the use of 'appropriate' peer-reviewed scientific literature in the development of the health app; 3. for technology: emerging criteria include robustness and interoperability with EHRs and The emerging ISO standard

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		includes the criteria of application size; 4. for security/privacy: compliance with national and EU legislation governing privacy and data-security (GDPR) and for USA the Health Insurance Portability and Accountability Act (HIPAA), implementation of ISO/IEC 27001, The emerging ISO standard suggests criteria such as protection against theft and viruses, signaling of breaches, authentication, data sharing, and maintenance; 5. usability (demonstration of user-center design, accessibility standards (WCAG), and development with iterative/agile principles): The emerging ISO standard (SE, NL) considers functionality, aesthetics, and availability in multiple languages

King, D.R., et al., Methods for Navigating the Mobile Mental Health App Landscape for Clinical Use. Curr Treat Options Psychiatry, 2023: p. 1-15. [14]	Mental health and wellness apps on the market	1) American Psychiatric Association (APA) App Evaluation Model: developed by John Torous' Digital Psychiatry Lab at Beth Israel Deaconess Medical Center (BIDMC) in 2019. It evaluates apps on 5 levels: 1. accessibility and background, 2. privacy and security, 3. clinical foundation, 4. engagement style, and 5. therapeutic goal. The idea is that if an app does not meet criteria at the lower level, no further app evaluation is necessary. The focus was on creating a data-driven tool that relied on objective evidence rather than subjective qualities and expert consensus. Numerical scores were avoided to maintain validity in a dynamic app marketplace that is constantly undergoing updates and changes 2) They describes Frameworks for user self-evaluation of the app, databases or "evaluation hubs" that are freely available for use by the public to operationalize the process of app evaluation: 1. mHealth Index and Navigation Database (MIND) is one such database that is based on an expanded version of the APA App Evaluation Model with 105 questions; 2. some clinics employ digital navigators who utilize these tools to create a list of apps that are then approved and authorized for use by the institution;

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Hoogendoorn, P., et al., What Makes a Quality Health App-Developing a Global Research-Based Health App Quality Assessment Framework for CEN-ISO/TS 82304-2: Delphi Study. JMIR Form Res, 2023. 7: p. e43905. [9]	The European Commission commissioned the European Committee for Standardization (CEN-CENELEC) to develop technical specifications for Wellness and Medical Apps for assessing quality. In line with CEN/TC 251 business plan, collaboration was sought with international standard bodies, such as International Standard Organization (ISO), International Electrotechnical Commission (IEC),	CEN-ISO/TS 823904-2:2021 – Part 2: Health and wellness App – Quality and reliability: framework of 81 questions. 67 (83%) of which impact the scores of 4 quality aspects: “Healthy and Safe”, “Easy to use”, “Secure Data”, and “Robust Build” (Appendix 8). Manufacturers estimated 2-4 days to complete the assessment and gather evidence.

	making the initiative a global activity	
Bohm, A.K., et al., Real-World Evidence of User Engagement With Mobile Health for Diabetes Management: Longitudinal Observational Study. JMIR Mhealth Uhealth, 2020. 8(11): p. e22212. [36]	They investigated diabetes chronic patient engagement through RWD collected by Novo Nordisk's Cornerstones4Care (C4C) patient support app	They proposed a framework to evaluate engagement of technology as a progress comprising 4 distinct stages: point of engagement, period of sustained engagement, disengagement, and reengagement. They established 6 metrics capturing different aspects of user engagement

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Debong, F., H. Mayer, and J. Kober, Real-World Assessments of mySugr Mobile Health App. Diabetes Technol Ther, 2019. 21(S2): p. S235-S240. [35]	Self-management goals and improve the quality of diabetes care	Proposal of the Net Promoter Survey (NPS) to evaluate the user satisfaction: NPS is a recognized survey tool that assesses satisfaction on a 1-10 scale based on customer responses to one key question: How likely is it that you would recommend [product/brand name] to a friend or a colleague? The NPS is calculated by: 1) grouping people in 3 groups: promoters that are people loyal enthusiast (score 9-10); passives that are satisfied by not enthusiastic (score 7-8); detractors that are unhappy users (score 0-6); 2) by subtracting the percentage of detractors from the percentage of promoters. Scores can range from -100 (100% of detractors) and 100 (100% promoters). We can compare NPS with Netflix, Apple.

Table A 7: Tools and Frameworks for mHealth development

Reference	Tools/frameworks for development
Fujio, K., et al., Patient and public involvement in mobile health-based research for hay fever: a qualitative study of patient and public involvement implementation process. Res Involv Engagem, 2022. 8(1): p. 45. [38]	Implementing the principles of patient and public involvement (PPI) in the development of our app: development of hay fever App (AllerSearch) including PPI in development and evaluation. Framework description: STEP 1) opinion exchange on smartphone App and exploration of unmet medical needs; STEP 2) research and planning; STEP 3) evaluation of prototype apps; STEP 4) development of AllerSearch and implementation of validity study; STEP 5) implementation of large-scale cloud-based clinical research; STEP 6) understanding diversity and generating evidence; STEP 7) publication and dissemination of research results; STEP 8) Evaluation of results and PPIs. These steps are based on PPI Guidebook published by Japan Agency for Medical Research And Development (AMED) in 2019. After each meeting, an interactive evaluation on the meeting from both the PPI contributors and researchers was conducted through questionnaires. At every step, the PPI contributors participated.
Essén, A., et al., Health app policy: international comparison of nine countries' approaches. npj Digital Medicine, 2022. 5(1). [21]	They showed different countries criteria to evaluate health App. These frameworks of evaluation can be taken in account during the App Development (See column "Tools/frameworks for quality assessment" of Table 6, [21])

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Leiner, J., et al., A Digital Infrastructure for Cardiovascular Patient Care Based on Mobile Health Data and Patient-Reported Outcomes: Concept Details of the Helios TeleWear Project Including Preliminary Experiences. JMIR Form Res, 2023. 7: p. e41115. [5]	Phase 1: beta-testing (The study was preceded by a beta-testing phase with preselected users to test the app's usability and implement technical adaptions within the app or clinical frontend); Phase 2: a feasibility study evaluates ECG and PROM transmission using wearables accompanied by a smartphone app in a real-world setting and forms the basis for the initiation of an Randomized Clinical Trial (RCT) that includes patients with Atrial Fibrillation (AF) of the Helios hospital network. The primary end point is the number of transmitted ECG recordings. Secondary end points include the number of completed PRO questionnaires, PROM and ECG evaluations by study physicians, symptom-rhythm correlation (ECG-PROM), type of response to the user and way of making contact, and user satisfaction with the app; Phase 3: RCT of TeleWear-AF is a multicentred, interventional, open-label, parallel-group randomized controlled trial with superiority design. Phase 4: application in clinical practice is considered

Fillo, J., et al., Simplified Novel Application (SNApp) framework: a guide to developing and implementing second-generation mobile applications for behavioral health research. Transl Behav Med, 2016. 6(4): p. 587-595 [11]	SNApp development framework, for research, is composed of 4 phases: PHASE 1 - information and resource gathering: a) consulting with developers with expertise; b) build an integrated project team, with developers in the core team; c) established priorities of project, because a clear picture can be useful for not changing features during the development. More generalized app architecture helps to minimize the impact of future devices and operating system changes; however, more generality can be more difficult to put in place; d) gather info from the target user population at early stage can help researchers to target parameters of the app and test the acceptability of its design. Suggestion: create a focus group to collect some info, for example comfort with mobile devices and the app (researchers should not assume tech proficiency among participants), willingness to have app installed on the phone (if the user smartphone will support the app and the security requirements of your institutional review board (IRB)), importance of device features and accessories, obstacle to protocol adherence (how potential users will use the device and potential obstacles to adhere to study protocol, such as work-related restrictions. E.g.: authors gave smartphone "skins" to increase the appeal and to increase the security in bringing phone all day); e) human subjects considerations regarding mobile device data protection requirements, if use local storage, if transmit data encrypted without storage. PHASE 2 - software and hardware decisions: a) choose the software for app development: prepackaged software solutions (skeleton of the App and you can put contents, such as surveys questions, etc...), for example Apple Research

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	Kit; or working with software developers: a software developer team can build an app precisely suited to researchers needs. Important considering the difficulty of developing from scratch; developing your own app without expert developers. Google and Apple provide materials to assist with App Dev; b) choose the hardware: example, ability to interface with other devices (e.g. accelerometers), to upload or download data via wi-fi, storage capacity... Selecting a device: for example, participants own device, or give a research device (reducing bias); user-specific considerations: consider the context in which the app and device will be used (is there internet connection?). PHASE 3 - software development and testing: a) consult best practices for software development: we recommend consider variants of AGILE. AGILE is based on iterative and incremental development cycles; app requirements and solutions evolve through collaboration among key members of the project team. AGILE has implication on time, because you need to test every time the changes; b) thoroughly test the app: testing process should ensure that the app works as intended, investigating different ways the user can interact with the app and device; seeing conditions of crash/fail. The test should involve different types of users (project team; end-users; colleagues less familiar with the app). Testing should be conducted iteratively and systematically, discovering problems and fixing them, and so on. Important also to find out requirements for maintenance: updates of software/operating systems must not affect app functions;

	c) Human subject considerations: - protect participant data: researchers should use multi-layers of security (password protections, encrypting the data on the device, disable camera, internet, ...); -protect non-consenting others: information can be gathered inadvertently from individuals who have not consented to participate (aka collateral participants). They consider several steps to reduce this risk: password-protecting the device, explicitly training users in the safe and responsible use of the device and App (including not sharing the device with others). They gave participants the possibility to delete any texts or sound files that could contain info about non-consenting others. PHASE 4 Study start-up and implementation: a) Pilot the App: pilot study with a fully functioning app to test the final app, refining training, and technical assistance materials; b) Train participants: training all participants (including "tech savvy" individuals) in the use of app, including what participants should use the device for, what they should not user it for, and steps to ensure that the device functions as intended in the field. They implemented a multiple-choice test in the initial training session. Researchers should anticipate that the development of training materials/procedures will be iterative, based on feedback. c) Provide technical support: considering budget for technical support (e.g., well-trained research assistants or graduate students). d) Human subject considerations: researchers should continuously monitor the quality and content of data collected to identify app and device malfunction.

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Wilhide Iii, C.C., M.M. Peeples, and R.C. Anthony Kouyate, Evidence-Based mHealth Chronic Disease Mobile App Intervention Design: Development of a Framework. JMIR Res Protoc, 2016. 5(1): p. e25. [10]	"Waterfall" Framework composed of 7 domains. The first 3 domains are strategic and were determined through interaction with external stakeholders: 1) Value drivers: entities that increase the value of a product/service. Examples for an mHealth product can include improved health for individual or population, improved access to care, or reduced health care costs. Value drivers set the course for the development of the mHealth solution, and in turn, dictated subsequent elements of the "waterfall" (sequence of steps). 2) Outcomes and Metrics: desired results of the program, and generally, can be short (e.g. knowledge, attitudes), intermediate (e.g. self-care behaviors), or long term (e.g. A1c), depending on the objective, length of the program, and expectations of program/interventions. The Metrics are the measurement aligned to industry-recognized quality metrics to facilitate the demonstration that interventions have an impact. 3) Program Goals for the Key Stakeholders: key stakeholders are those users that the system is designed to support directly. What intended users should accomplish via product use are the program goals. Domains from 4th to 6th define the Intervention Plan divided into 3 subdomains, for the behavioral intervention through the product: 4) Behavioral Domains, Essential Behaviors, Supporting Actions and Determinants: behavioral domains are the categories of self-management behaviors, and encompass essential behaviors ("... that should be emphasized through program interventions because of its impact on public health, its measurability, and its feasibility to be performed by patients, caretakers and/or health workers."), their associated supporting actions, and determinants. Behavior is associated to improvements in clinical outcomes or longer-term health impact or quality of life.

	5) Multidimensional Profile: segmentation approach that drives the individualization of a user's experience through customized delivery of interventions via features and tailored message content. Content tailoring includes targeted message based on demographic characteristics, personalization (e.g. incorporating first name into message), or tailoring content in response to assessments, captured data, or the context in which data was captured (e.g., bedtime, blood glucose [BG] reading). 6) Evidence-Based Clinical/Behavioral Interventions: evidence-based interventions are those that have been identified as effective for achieving outcomes, and are best practices, which have been peer-reviewed and evaluated for effectiveness in improving health outcomes. The 7th domain is represented by the App Feature/Content: following the "waterfall" process, intervention plans were then translated into product features and content identified to deliver optimal outcomes to meet product/program objectives. Product features, functionality, and content are designed to deliver program interventions in the most effective means possible, by leveraging state-of-the-art technology with the goal of a highly engaging user experience. These features are derived from previous domains and developed following an iterative process.

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https://www.utwente.nl/en/bms/ehealth/cehres-roadmap-toolkit/cehres-phases/	The CeHRes Roadmap serves as a guideline for eHealth development, implementation, and evaluation. Existing evidence-based activities, models, frameworks and methods derived from persuasive design, participatory development, human centered design and business modelling serve as the theoretical background of the Roadmap. All of this is translated into five intertwined phases and connecting cycles. 1) contextual inquiry: the design team must get an understanding of prospective users and their context and analyze the strong and weak points of the current provision of care. 2) Value specification: determine which values the different stakeholders deem important. These values and prospective users' need and wishes need to be translated into user requirements. 3) Design: based on the requirements, (a prototypical version of) the technology can be developed. The roadmap advocates the application of cooperative design in which the design team creates the technology with prospective users and stakeholders together. 4) Operationalization: now, the technology is launched, marketing plans are set into motion, and organizational working procedures are put into practice. 5) Summative Evaluation: finally, the eHealth technology is evaluated: how is it being used and what is its effect on patients and healthcare? Suggestion: the products created in each phase should be the subject of Formative Evaluation, aimed at gathering input for improving the product. The CeHRes roadmap is created for developers (e.g., technicians, designers, healthcare professionals), researchers, policy-makers, and for educational purposes (e.g., students, healthcare providers).

	Formative Evaluation: Within this process, eHealth development requires continuous evaluation cycles, both a) during eHealth development, and b) at the end of the development and implementation, which is often referred to as formative evaluation. The formative evaluation has two main goals, both related to the development process: 1) Checking whether the outcomes of previous phases have been accounted for in the current phase, and that the outcomes of all phases are related to each other; 2) Using methods to gather information from the stakeholders and context to continuously include their perspectives in the activities and outcomes of the development, implementation, and evaluation. First, it can be conducted as a backward evaluation, which occurs at the end of a specific development phase to check whether the goals as set at the start of that phase have been reached and have been accounted for. Second, it provides information on the current state of the development process and how to make improvements before moving on to the next phase (forward evaluation). The formative evaluation of eHealth is iterative and is the backbone of the development of eHealth technology. Formative evaluation aims to monitor whether a project is still on track, detect problems as early as possible, solve these problems as soon as possible, and to make sure that the relationship between the technology, stakeholders and context is guaranteed.

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Khatiwada, P., et al., Patient-Generated Health Data (PGHD): Understanding, Requirements, Challenges, and Existing Techniques for Data Security and Privacy. Personalized Medicine, 2024. 14(282). [23]	Security & Privacy Tools & Frameworks for implementing Personal-Generated Health Data Systems: 1) Restrict Access to Data and Applications: - Multifactor Authentication (MFA) (passwords, fingerprints, ect…); - Role-Based Access Control (RBAC) according to responsibilities; - Least Privilege Principle: access to level required to perform duties; - Routine Audits: identifications of security vulnerabilities and control of access protocols; - Firewall: measures against illegal network invasions; - Virtual Private Networks (VPNs): security of remote accesses; - Continuous Update and Software Maintenance. 2) Implement Data Usage Controls: - Robust Access Controls: restrict visibility to authorized users; - Encryption for data integrity; - Audit Trails: ensure accountability; - Adherence & Compliance to HIPAA and GDPR - Policies and Procedures continuously updated: to align with legal & ethical norms; - Training Person about Protocols; - Informing Patients about their rights and the extent of their control over personal data; - Involvement of Stakeholders; - Use of Feedback Loops; - Individual Access to PGHD in Real-Time and Electronically: transparency and data control;

	- Clarify Informed Consent Processes about data usage sharing and possibility to modify consent in a second moment; - Possibility to share data for research maintaining privacy. 3) Logs and Monitor Use: - Log Who and When PGHD are accessed; - Proposal of Machine Learning Techniques to identify access anomalies and data breaches. 4) Encrypt Data at Rest and in Transit: - Encryption of Non-Data Files: proposal of two-level encryption with passcode lock 5) Secure Mobile Devices: - Problem of Using Mobile Devices by Healthcare Providers and Patients (device theft, insecure apps, inadequate security management); - Recommendations about administrative measures, physical security, secure data exchange, updates, training personnel. 6) Mitigate Device Connected Device Risks: -Devices connected to internet are vulnerable, thus, it is better to be compliant with regulations (e.g. FDA). 7) Conduct Regular Risk Assessments: - Proposal of a Framework for Risk Assessment called Integrated Security, Safety, and Privacy (ISSP) Risk Assessment Framework for medical devices with respect to device classification: systematic approach that uses calculation of ISSP score and it is based on FDA recalls and incorporates Common Vulnerability Scoring System (CVSS). 8) Educate Healthcare Staff: - Training programs about cyber security

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	They proposed also a Privacy & Security Framework by following the recommendations in Table 7 and 8 of [21]: 1) Data Collection Policies: document all processes and lifecycle; 2) Consent and Transparency: explicit consent mechanism & transparence about data processing; 3) Secure Data Transmission: end-to-end encryption; 4) Robust Authentication: MFA, biometrics, identifiers, etc…; 5) Data Minimization: only necessary data collected; 6) Data Storage Security: use certified encrypted databases on cloud; 7) Endpoint Security: ensure mobile app security; 8) Network Security: protect networks over which PFHD are transmitted (firewall, intrusion detection systems,, secure wi-fi protocols, penetration tests, etc…); 9) Data Anonymization: remove or obfuscate personal identifiers (differential privacy techniques); 10) Regular Security Audits: periodic & compliance to regulations; 11) Data Integrity Checks: use of checksum of PGHD during lifecycle; 12) Secure Application Development: security by design and use of strong test; 13) Disaster Recovery and Business Continuity: rapid data restore plans; 14) Legal & Regulatory Compliance: compliance with GDPR, HIPAA, or HITECH, or other laws; 15) Training and Awareness: training programs for all stakeholders. 16) Federated Learning: if using ML or AI models, sharing if only models and not data;

	17) Blockchain Technology: ensure system trustability, using blockchain as PGHD track and consent ledger; 18) Homomorphic Encryption: leave data encrypted during analysis; 19) Secure Multi-Party Computation: use of private input to a shared function; 20) Differential Privacy: add statistical noise to data; 21) Zero-Knowledge Proofs: test data integrity and authenticity preserving privacy; 22) Advanced Persistent Threat (APT) Protection: measure against cyber-attacks: 23) AI Security Audits: if AI is used; 24) Decentralized Identify Management: patients control over their PGHD and ID (e.g. using Blockchain); 25) Continuous Security Monitoring: detect and respond to anomalies in real-time.

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Table A 8: Real-world use cases and architectures of RWD App ecosystem

Reference	Example
H. op den Akker, et al., Digital Therapeutics: Virtual Coaching Powered by Artificial Intelligence on Real-World Data, Frontiers in Computer Science 2021 Vol. 3. [18]	Example of the European research project RE-SAMPLE (REal-time data monitoring for Shared, Adaptive, Multi-domain and Personalised prediction, and decision making for Long-term Pulmonary care Ecosystems) ecosystem and its use cases, using RWD for digital therapeutics/clinical intervention. Proposal of an architecture: two user-interface components: the Healthentia Mobile App, which is the main point of entry to the system for the primary end users (Subjects or Patients), and the Healthentia Web Portal, which is the main entry point for Healthcare Professionals. The central component—the User Data Service—is a cloud service that handles storage of- and access to all the different types of data that is collected or generated by this Digital Therapeutics platform. The main digital therapeutic functionalities are provided by the five surrounding services: Real World Data Collection Service, Learning- and Intelligent Decision Services, Clinical Pathway Services and the Virtual Coaching Services.

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Wehrle, K., et al., Implementation of a data control framework to ensure confidentiality, integrity, and availability of high-quality real-world data (RWD) in the NeuroTransData (NTD) registry. JAMIA Open, 2022. 5(1): p. ooac017. [12]	Description of entire data management and control RWD ecosystem for multiple sclerosis, through data control workflow and data journey. They described the data journey from the gateway into a DB to the move of data into the Analysis module, underlying the control data process at each step. In the data journey, they described also the applications to preserve data privacy (pseudo anonymization, GDPR compliance, etc...).

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Leiner, J., et al., A Digital Infrastructure for Cardiovascular Patient Care Based on Mobile Health Data and Patient-Reported Outcomes: Concept Details of the Helios TeleWear Project Including Preliminary Experiences. JMIR Form Res, 2023. 7: p. e41115. [5]	TeleWear approach aims to develop, implement, and study an infrastructure for remote patient management that is based on 2 key elements: mobile-collected health data and PROs. Patients use a smartphone app that acts as a transmission platform and can integrate data from various health apps on the patient's private smartphone, such as the smartphone's built-in health data apps as well as apps for ECG recording with an accompanying wearable (Figure 1A). Furthermore, patients are asked to answer distinct questionnaires for PRO collection (Figure 1B). Collected data will then be transferred to a clinical frontend and reviewed by designated cardiologists using specific tools for evaluating recorded health data and PROM scores (Figures 2 and 3). The app is equipped with an application programming interface (API) that allows extensive customization; the integration of different data sources (health apps) and the addition of questionnaires are possible at any time. Because of this technical design, patients can provide comprehensive health data measurements to the clinical frontend. The app: The TeleWear app and the clinical frontend were developed using an existing API (Thryve mHealth Pioneers GmbH) that allows the integration of apps and corresponding wearables by various manufacturers. Through this approach, linkage of other health apps that record data such as blood pressure, activity, or oxygen saturation is possible at any time as is the addition of other questionnaires and PROMs. However, for the purpose of the feasibility study, only the transmission of ECGs and a predefined set of PROMs is implemented. Currently, the app allows data exchange with Apple Health (Apple Inc) and Withings Health Mate (Withings; Figure 1A). Integration of other apps is part of further development. ECGs (and health data) recorded by manufacturer-specific wearables

	are saved within the respective app and then transferred to the TeleWear app, which allows transmission to the Leipzig Heart Institute (Figure 6). ECGs are transmitted in .xml-file format, which can be viewed and analyzed within the clinical frontend (Figure 3A). PROMs are stored locally within the app. All data are transferred pseudonymized. The TeleWear app itself does not provide any medical advice or automatic ECG or PROM evaluation and only serves as a transmission tool. Therefore, the app does not constitute a medical device and requires no CE mark, which was confirmed by the responsible ethics committee (for the vote, see above). The required app is available for free from app stores on iOS and Android devices; Clinical frontend: The clinical frontend was specifically developed for the TeleWear platform using the Next.js (Vercel Inc) web development framework. It can be accessed via every web browser within the Helios network with a personalized login. Login data is provided only for study personnel. The TeleWear clinical frontend comprises an overview of all activities by study participants, an ECG evaluation tool to perform measurements, and a PROM score viewer (Figures 2 and 3). Those scores are calculated automatically based on instructions provided by the publishers of the respective PROMs. If one questionnaire is answered multiple times, changes in PROM scores (improvement or worsening) are displayed by the system so that physicians can assess potential changes in the participant's health status (Figure 2B). Study personnel contact the user via the provided contact form directly within the clinical frontend if feedback is desired and provide the physician's evaluation and recommendations for further proceedings.

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Sivan, M., R.n.R. Lawrence, and P. O'Brien, Digital Patient Reported Outcome Measures Platform for Post–COVID-19 Condition and Other Long-Term Conditions: User-Centered Development and Technical Description. JMIR HUMAN FACTORS, 2023. 10(e48632). [39]	They described before the design journey: 1) Requirements Analysis: use of CE-marked ELAROS platform of digital health company 24/7 Ltd, a Digital Bladded Diary (DBD) Patient Reported Outcome Measures (PROM) platform. They adapted these platforms that administered PROMs about lower urinary tract symptoms to the needs of people with Post Covid-19 Condition (PCC). 1.2) Architecture: the app-based DPROM platform was written using web-technologies via the Apache Cordova (Adobe, Apache Software Foundation) framework for Google Android (minimum operating system version 7 Nougat), Apple iOS (minimum operating system iOS version 9), and through a web-based portal via a Chromium-based browser. They wanted the patients use mobile devices, but, it they cannot do so, or they prefer to use desktop or laptop, they may access a web-based version of mobile app, that can be used also by Healthcare Practitioners (HCPs) to complete PROMs on patients' behalf during tele-assessment. Patients could complete paper version of administered C19-YRS (Yorkshire Rehabilitation Scale) PROM, and upload it via the mobile app or web app. The web-portal is cloud-based and can be accessed by different supported Chromium-based browsers (Chrome, Firefox, Edge, and Safari). The web-app was written in a combination of SASS, HTML, JavaScript, and PHP, based around LAMP (Linux, Apache, MySQL, PHP/Perl/Python) technology stack. The mobile device and browser communicate using a physical app server via an app program interface, which communicates with a database server also managed within same infrastructure. All users access a single app server and database with restricted access to their treating clinic set up by ELAROS. 1.3) Data Flow: 1.3.1) Authentication: people with PCC are registered by HCPs or clinical staff members on the ELAROS platform using minimum patient identifiable: name, date of birth, gender, and health

	ID number such as the English National Health System (NHS) number or Scottish Community Health Index number. This generates unique patient login details (username and pin), that are shared with the individual with PCC and used to log into the mobile or web app. 1.3.2) App use: after the login, the users can complete PROMS through the app at the time points defined by their clinical team, with support of automatic reminders which can be configured by the clinic. 1.3.3) Data Processing: the system processes their data and stores it in a database alongside the patient's details for staff to access and identify the individual records. 1.3.4) Data Access: the patient can access recorded data via the app to see assessment history and trends. The clinical teams can use the web portal to see the individual or overall patient reports and manage the clinic. This info can be exported into a summary PDF report or as a comma-separated values (CSV) data file which can be uploaded to the patient's Electronic Health Record (EHR), depending on the file formats the EHR accepts. 1.3.5) Data Use for Research: a research version of the web portal is available to view pseudo anonymized data from patients who have consented to sharing their data with authorized researchers, enabling local or externally approved research teams to access clinical data for research at an individual, local, and or national level. 2) Design of Outcome Reports: additional clinical measurements and demographics were requested to be collected through the platform to gain better understanding of patient's' overall health and to meet local, regional, and national reporting requirements to undertake routine service audits or evaluation of patients being seen in services and in research. Detailed metrics and summary data collected and processed by the DPROM platform are presented to staff in the clinical web portal to analyze internally to help guide conversations with people with PCC and deliver clinical care, with each tool displaying data in different ways. A mechanism was required to export data from the DPROM platform

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	in an accessible and easy-read format to upload to local EHR. This clinical info is compiled into a summary report and exported from DPROM platform as PDF, which can be uploaded to patient's EHR at any time, enabling staff to take a "snapshot" of the patient's condition at different timepoints which can be stored permanently on local EHRs for other clinic access. Alternatively, raw assessment data can be exported as CSV file for individual users or manually transcripted into the EHR platform, as different EHR system accept different file formats. 3) Patient and Public Involvement (PPI): as [28], they involved weekly or fortnightly PPI at different clinical sites remotely to help inform clinics on how to develop local pathways and services to offer adequate care to patients. PPI groups served as natural target to introduce DPROM platform to gather early feedback and input to the discovery, design, and development phases of platform to rapidly develop for live service. From Design to Key Requirements: 1) people with PCC should directly respond to questionnaire on the system, without paper forms, and have to send them back to the service or clinicians; 2) real-time assessment should be performed by clinicians, without waiting for forms from patients; 3) feedback on the info collected from questionnaires should be returned to the respondent in an easy-to-understand way, improving patient's self-management; 4) the system should include self-management resources or direct users to resources available elsewhere; 5) PROMS need to be PCC specific and comprehensive; 6) PROM data should integrate with existing HER in a standardized manner; 7) consent from respondents should be gathered to use their data for approved research or service audits and evaluation 8) user data should be automatically pseudo anonymized (ie, the removal of identifiable information) for use in research studies; 9) analysis of summary statistics should

	be generated for the entire cohort of users in the system in an easy-to-understand format for service providers and commissioners. From Key Requirements to Development: 1) the Web App: an on the internet clinical web portal used by staff within PCC clinic to oversee patients, analyze assessments, communicate with the patient, and extract data for permanent storage in EHRs. This is hosted on Cloud and it is the central PCC digital "hub" for clinics to assess to register new patients who are referred to the clinic with an account, administer a selection of PROMs with preconfigured automatic reminders, analyze health data as it is received and processed into a graphical or tabular format, communicate with the patient via 1- or 2-way messaging, and extract data ready for upload and permanent storage in the patient's EHR managed by clinic. The platform generated a radar chart, or spider chart, to illustrate the patient the multiple symptoms recorded in the C19-YRS and how they fluctuate over time. 2) the Mobile App: a patient-facing app used to complete assessments, communicate with the clinic, and access rehabilitation resources between appointments. This can be accessed on mobile by the patient, if they are confident with this technology, and self-report information about their symptoms and which to access educational and rehabilitation resources available within the app for self-monitoring and self-management purposes. Alternatively, they can access the same app on the internet via web-based version. The clinical staff too can access the web-based version to sign into the patients' behalf to complete assessments with a patient or their care or guardian as part of a tele-assessment, useful to patients who may be digitally excluded. This app included also numerous translatable support resources to help patients and carers to educate themselves and access rehabilitation resources around different elements of their condition in an easy-read, mobile optimized or on the internet

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	format. The resources curated and packaged by ELAROS have been contributed by various NHS trusts who developed these resources to support their patients. This provided assurance on content validity and clinical quality, promoting sharing of best practices and acquired knowledge on how clinics are approaching this new condition. 3) Research Version of the Web App: research version of clinical portal to authorized staff to access pseudo anonymized data sets from patients who have given consent for sharing their data for appropriate means, for example as part of a regional service evaluation carried out by staff external to the clinic, or as a part of national research projects. This automatic pseudo anonymized and provision of consent remotely through the platform is timesaving and less burdensome on research teams traditionally using paper forms through the post and manually logging information into a computer; 4) PROMS Available on The Platform: 30 PROMs and related health questionnaires, with additional measures being requested inside and outside of United Kingdom (Textbox 1 in [39]). 5) Summary Reports for EHR: the platform generates summary reports that can be uploaded to patient EHR. Aggregate reports for the entire service caseload can also be generated and used for service evaluation of outcomes and sharing with national regulatory authorities such as NHS England. From Development to Usability Evaluation: the platform was used by 46 PCC centres in England, 2 centres in Scotland, and 1 centre in Wales, serving approximately 10000 users across 32 NHS trusts and health boards at the time of writing. A sample of quotes (anonymized) from patients and staff using the system is summarized in Table 1 of [39].

B Appendix B

Appendix B reports the Table B 1 showing the uMARS median scores obtained for each item among all the BRCApp users.

Table B 1: Item uMARS scores (italian version), expressed as Median with 25th and 75th percentiles (25th;75th)

uMARS Item	Question Text	Median (25th;75th)
1	SEZIONE A: Coinvolgimento. Intrattenimento: l'App è divertente/simpatico da usare? Ha elementi che la rendono più divertente di altre app simili?	3.00 (3.00;4.00)
2	Interesse: l'App è interessante da usare? Presenta le sue informazioni in un modo interessante rispetto ad altre app simili?	4.00 (3.00;4.00)
3	Personalizzazione: ti consente di personalizzare le impostazioni e le preferenze che desideri come le vorresti tu (ad esempio suoni, contenuti e notifiche)?	3.00 (2.00;3.00)
4	Interattività: consente l'interazione dell'utente, fornisce feedback (es. contenuti e/o informazioni personalizzate basate sul tuo utilizzo), contiene suggerimenti (promemoria, opzioni di condivisione, notifiche, ecc.)?	3.00 (2.25;4.00)
5	Gruppo target: il contenuto dell'App (grafica, lingua, design (interfaccia)) è appropriato per il pubblico a cui si rivolge?	4.00 (3.00;4.75)
6	SEZIONE B: Funzionalità. Prestazioni: la precisione / velocità delle funzioni dell'App (caratteristiche) e dei componenti (pulsanti / menu) funzionano?	3.00 (3.00;4.00)
7	Facilità d'uso: quanto è facile imparare ad usare l'app; quanto sono chiare le etichette (sezioni) del menu, le icone (immagini) e istruzioni?	4.00 (3.00;4.00)

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8	Navigazione: muoversi tra gli schermate ha senso; L'App ha tutti i link necessari tra le schermate (la navigazione funziona tra tutte le sezioni/schermate della App)?	4.00 (3.00;4.00)
9	Progettazione gestuale: i tocchi /gli strisciamenti / i pizzichi / gli scorrimenti hanno senso? Sono coerenti tra tutti i componenti / schermate?	4.00 (3.00;4.00)
10	SEZIONE C – Estetica. Layout (elementi grafici nelle pagine): disposizione e dimensioni di pulsanti, icone, menu e contenuti sullo schermo adeguata?	4.00 (3.00;4.00)
11	Grafica: quanto è alta la qualità/risoluzione della grafica utilizzata per pulsanti, icone, menu e contenuti?	3.00 (3.00;4.00)
12	Visual appeal (estetica visiva): quanto è bella l'App?	4.00 (3.00;4.00)
13	SEZIONE D – Informazioni. Qualità dell'informazione: il contenuto dell'app è corretto, ben scritto e pertinente all'obiettivo/ all'argomento dell'App?	4.00 (3.00;4.00)
14	Quantità di informazioni: le informazioni contenute nell'app sono complete, ma concise?	4.00 (3.00;5.00)
15	Informazioni visive: la spiegazione visiva dei concetti - attraverso grafici / diagrammi / immagini / video, ecc. è chiara, logica, corretta?	4.00 (3.00;4.00)
16	Credibilità della fonte: le informazioni all'interno dell'app sembrano provenire da una fonte attendibile?	5.00 (5.00;5.00)
17	SEZIONE E - Qualità soggettiva della App. Consiglieresti questa app a chi potrebbe trarne beneficio?	4.00 (3.00;4.75)
18	Quante volte pensi che useresti questa app nei prossimi 12 mesi se fosse adatta a te?	4.00 (3.25;5.00)
19	Pagheresti per questa app?	1.00 (1.00;2.00)
20	Qual è la tua valutazione complessiva (con stelle) dell'app?	3.00 (3.00;4.00)
21	. SEZIONE F - Impatto percepito. Consapevolezza: Questa app ha aumentato la mia consapevolezza dell'importanza dei comportamenti salutari	3.00 (2.00;4.00)

22	Conoscenza: Questa app ha aumentato la mia conoscenza/comprensione dei comportamenti salutari	3.00 (2.00;4.00)
23	Atteggiamenti: L'app ha cambiato il mio atteggiamento verso il miglioramento dei comportamenti salutari	3.00 (2.00;4.00)
24	Intenzione di cambiare: L'app ha aumentato le mie intenzioni/motivazioni per affrontare i miei comportamenti salutari	3.00 (2.00;4.00)
25	Ricerca di aiuto: Questa app mi incoraggerebbe a cercare ulteriore aiuto per affrontare i comportamenti salutari (se ne avessi avuto bisogno)	3.00 (2.00;4.00)
26	Modifica del comportamento: l'uso di questa app aumenterà / diminuirà i miei comportamenti salutari	3.00 (3.00;4.00)

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