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mHealth Data for Real World Evidence in Regulatory Decision Making

An expert review report for the HMA/EMA Big Data Steering Group - 2024

Executive Summary

With the increasing use of digital tools for personal health monitoring, they have become an essential part of modern healthcare delivery and are now being used more than ever in clinical research and drug development.

In the last five years, the European Medicines Agency (EMA) has seen an increase in the number of products and applications in its pipeline including digital technologies. The role of digital, specifically mobile devices in drug development and regulation, is only expected to grow. Therefore, it is necessary for regulators to proactively examine the impact of digital tools and data on regulatory decision-making to know when and for which purposes these novel data are reliable and useful. Working towards fulfilling its Big Data vision, the joint HMA/EMA Big Data Steering Group (BDSG) is therefore investigating the utility of mobile health (mHealth) data for regulatory decision-making.

mHealth tools such as smartphones, health applications, smartwatches and other wearables can generate a large variety of detailed patient data like heart rate, body temperature, and sleep quality while users go about their daily routines. They provide measurements of patient function in the real-world on a more granular level than any other real-world data (RWD) source used in medicine regulation. mHealth data generated by these tools shows potential for enhancing the clinical evidence used in regulatory decision-making, yet notable challenges may hinder their utility, in particular around data quality and protection of patient privacy.

This expert report reviews relevant literature related to the use of mHealth data in the context of medicine regulation and aims to discuss its utility for regulatory uses. While mHealth tools can also be used during clinical trials, this report focuses on their use in real-world settings (i.e. in clinical care or the daily life of patients), to generate RWE for regulatory decision-making. 82 scientific articles retrieved between December 2023- January from the Embase database were included for this review and allowed to gather examples of cases where mHealth data was used to fulfil needs that could be applicable in the future to support regulatory decision-making.

As RWD, mHealth data was found to be useful for EU medicine regulation in three domains:1) to support planning and validity of applicant studies, 2) to support the understanding of clinical context, and 3) to investigate associations of products on safety and efficacy outcomes and impacts of regulatory actions.

1. mHealth data was found to be particularly useful to inform the design of applicant studies by informing eligibility criteria and the choice of study measurements meaningful for patients. mHealth data can also be linked to other patient health databases like electronic health records (EHRs) and Registries and thus substantiate the assessment of representativeness and external validity of completed applicant studies.

2. To support the understanding of clinical context, mHealth data can provide valuable insights into disease spread and progression through wearable sensors measuring patient symptoms and health apps tracking the spatial prevalence of disease. Mobile applications created for physicians can also provide insights into treatment patterns and medicine prescription rates, both helpful in investigating current standard of care and clinical management across Europe. Additionally, via medication tracking apps and wearables, mHealth data can give more detailed insights into patient's actual medication intake in the real-world and better reflect the habitual and daily experiences of patients.

3. mHealth data from applications for adverse drug reaction (ADR) reporting and wearables measuring physiological changes seem to be particularly useful in post authorisation

monitoring by supporting ADR characterisation and signal detection. Data on ADRs can also be used to assess the impact of regulatory actions to reduce the rates of ADRs, though little evidence for this area was found. Finally, mHealth data can be useful in assessing the effectiveness of medicines through measuring biomarkers associated with disease and recovery while continuous data collection allows unmatched insights into the day-to-day variability in patient response.

While mHealth data was found to be useful to address several regulatory needs, challenges and opportunities were also identified and these were organised into operational, technical, and methodological categories.

- Data protection, accessibility and a complex regulatory landscape were identified as main operational challenges. Data protection measures are implemented in various ways and for most, especially consumer mHealth tools, data protection standards are not met. The ecosystem for storing and sharing mHealth data is fragmented which restricts access. Moreover, the landscape for generation and use of mHealth data raises important considerations on regulatory acceptance. At the same time, opportunities in advancing the field exist in fostering better data protection for mHealth tools and leveraging initiatives working to increase access to high quality patient mHealth data and identifying the mHealth tools that are fit-for-purpose for the specific use case at hand.
- In terms of technical challenges, mHealth data quality can suffer from environmental conditions, the accuracy and placement of sensor and ability of patient to use the tool correctly. Interoperability of mHealth data is impacted by the different data sharing standards used by device developers and the sometimes unstructured and unlabelled data sets. However, many currently available mHealth tools have been shown to be accurate in a variety of conditions and are mostly easy to use, while novel approaches using artificial intelligence (AI) and machine learning (ML) techniques can be employed to tackle interoperability issues for example.
- Finally, several methodological challenges must be considered when using mHealth data. mHealth tools are equipped with different sensors and features depending on the device and brand and the measurements taken may not always reflect the concept of interest accurately, for example waving an arm up and down may increase step count measured by a smartwatch. Younger and wealthier populations are more likely to frequently use digital devices to measure their health, raising issues around the representativeness of mHealth data. However, given the opportunity of passive data collection capability of many mHealth tools, they can be specifically useful for collecting more complete data from specific populations, such as paediatrics, over an extended period. AI powered methodologies are also showing potential in analysing the large mHealth data sets effectively.

To conclude this expert review, a set of 7 points for consideration for future actions are proposed to increase the utility of mHealth data in regulatory decision-making. Primarily, better access to mHealth data must be facilitated. While the potential for increased access through established RWD pathways and directly from mHealth companies is recognized, this report promotes the collection of data directly from patients using mHealth tools. As such, a rather ambitious proposal for the establishment of a common European patient data platform is outlined. Such a platform would provide a stable and secure mechanism for patients to share data via mHealth tool, better reflect the diversity of EU population and facilitate health research, medicine regulation and policy making. The importance of engaging with all stakeholders while leveraging and highlighting other currently ongoing initiatives and work around mHealth data is underlined. Additionally, the current use of mHealth data in regulatory submissions is to be understood more clearly, while the next

steps should also focus on increasing confidence in digital data through fostering creation of and assessing more digital endpoints and mHealth data sources. A particular attention is to be placed on the protection of patient data and ethical considerations of secondary use of sensitive patient data in regulatory decision-making. This expert review shows that the recent years have brought immense innovation in the uses of digital tools and improved reliability of data collected using mHealth tools. Though much work lies ahead for the efficient and general acceptance of mHealth data for regulatory decision-making, these findings suggest that significant opportunities exist for the EU regulatory network to enhance medicine regulation by leveraging mHealth data.

Contents

List of Acronyms

Abbreviation	Definition
RWD	Real World Data
RWE	Real World Evidence
EHR	Electronic Health Record
EHDS	European Health Data Space
MAA	Marketing Authorisation Application
mHealth	Mobile Health
BDSG	Big Data Steering Group
COVID-19	Coronavirus Disease 2019
EMA	European Medicines Agency
HMA	Heads of Medicines Agencies
CTTI	Clinical Trials Transformation Initiative
PRO	Patient Reported Outcome
HCP	Health Care Provider
AI	Artificial Intelligence
ML	Machine Learning
PED	Patient Experience Data
QoL	Quality of Life
CT	Clinical Trial
API	Application Programming Interface
DVG	Digitale-Versorgung-Gesetz (The Digital Care Act (Germany))
PGO	*Persoonlijke Gezondheidsomgeving* (digital healthcare environment (the Netherlands))
ADR	Adverse Drug Reaction
SUD	Substance use disorder
IBS	Irritable Bowel Syndrome
RMM	Risk Minimisation Measure
DQF	Data Quality Framework
GDPR	General Data Protection Regulation
MDR	Medical Devices Regulation
HRQoL	Health Related Quality of Life
NHS	National Health Service (UK)
MKUH	Milton Keynes University Hospital
6MWT	Six Minute Walking Test
DNN	Deep Neural network
IHI/IMI	Innovative Health Initiative / Innovative Medicines Initiative
ITF	Innovation Task Force
ICMRA	International Coalition of Medicines Regulatory Authorities
SA	Scientific Advice
ISO	International Organisation for Standardisation

1. Scope and Objectives

This expert review report supports the delivery of the BDSG workplan 2023 to 2025 (HMA/EMA joint Big Data Steering Group, 2023). To further progress and strengthen the work already done to enable the use and establish the value of different types of RWD to support regulatory decision-making, the BDSG aims at looking further into how mHealth data generated in real life or in routine care could be useful in regulatory decision-making, and what could be possible points for consideration for future actions for their optimal use in the EU regulatory network moving forward.

mHealth can be broadly defined as the practice of using mobile technologies and digital interventions to support clinical care, research, or self-management to ultimately improve health outcomes (Donegan et al., n.d.). mHealth technologies range from body worn sensors (wearables) to mobile applications tracking health and fitness and the software and smartphones required to run them (Kakkar et al., 2018). Wearables can be defined as body worn devices or accessories equipped with sensors to measure various health related activities and outcomes (Babar et al., 2023). Two types of wearables are distinguished: research grade wearables designed and validated for health research purposes and often used in patient monitoring and clinical care, or consumer grade wearables available for individuals to purchase for personal use. Many consumer grade wearables however have become more and more reliable and accurate, facilitating their use in health research and healthcare decision-making (Seneviratne et al., 2023).

mHealth data is therefore defined as the information collected using mHealth tools and technologies. mHealth data can be continuous e.g. heart rate data measured over several days, or intermittent e.g. occasional measurements of symptoms logged by a patient manually when they arise. More information can be found in figure 1 below.

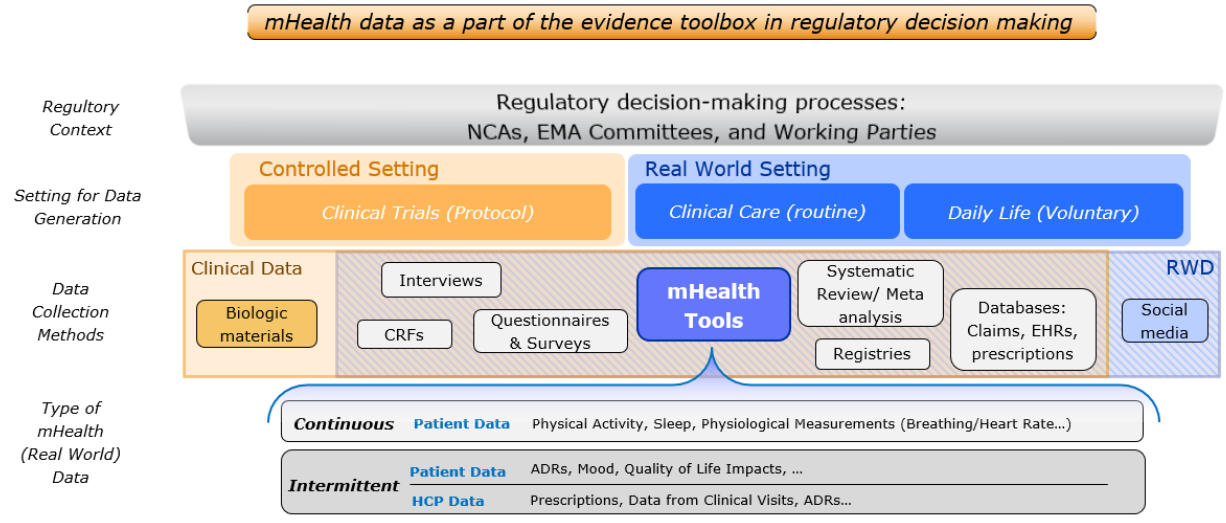


Figure 1. mHealth data in regulatory decision-making. The top layer of Figure 1 depicts how there are various regulatory bodies which leverage data for their decision-making processes. These data can be generated in a controlled setting via clinical trials for example, or in real world settings during routine clinical care or voluntarily by patients during their daily lives. mHealth tools are one of the tools and methods available in the data collection toolbox and can be used to collect either clinical data or real-world data (RWD). As RWD, the data generated by mHealth tools can be continuous, e.g. longitudinal tracking of users' heart rate, or intermittent, e.g. occasional ADR entries manually inputted by the user. Both patients and HCPs can generate and collect mHealth data.

Most often mHealth data is generated in numerical or text format but it can be in an image or audio format. mHealth data can capture a large variety of patient data, such as demographic, physiological changes related to disease(s) or treatment(s), patient experience data (PED), as well as socio-

economic and lifestyle data. Depending on the intended use of the mHealth tool and the setting to collect the data, mHealth data can be considered as RWD when mHealth data is generated during a patient's daily life or as part of routine clinical practice, or be considered as clinical trial data when generated in a controlled research setting during a clinical trial. In line with the mandate of the BDSG, this expert review report focuses on the utility of mHealth data generated in the real-world routine care context as one type of RWD for regulatory decision-making. The BDSG was consulted on the report between June-July 2024.

This expert review report aims to answer the following questions:

- How can mHealth data support regulatory decision-making? What are the regulatory use cases and additional value of mHealth data?
- Considering the latest technological, methodological and regulatory developments related to RWD and mHealth data, what are the current challenges and opportunities for the use of mHealth data in regulatory decision-making?
- What are the possible points for consideration for future actions to enable the use and establish the value of mHealth data into the EU regulatory decision-making?

2. Background

The vast leaps in digital technologies over the recent years have allowed for the scientific and regulatory community to look beyond traditional types of data for generating evidence to inform and support regulatory decision-making (Macdonald et al., 2021). More specifically, RWE are increasingly used in regulatory assessments to complement evidence generated through randomised controlled trials (Flynn et al., 2022).

RWD are data reflecting "real-world" patient characteristics in clinical practice. They include a large variety of data such as healthcare records, medical claims data, medication prescribing and dispensing data, socio-economic and lifestyle data, data from patient registries, patient experience data, health care services utilisation data, data collected with wearable biometric devices and genetic data.[1] RWD derived from registries, EHRs or insurance claims have already been used in marketing authorisation applications (MAA), to support the regulatory assessment or for post marketing surveillance purposes (Bakker et al., 2023; European Medicines Agency, 2023c; Flynn et al., 2022). Other RWD derived from social media or mHealth, though promising, are yet to be harnessed to their full potential for regulatory decision-making. As RWD, mHealth can capture diverse health related information depending on the context, and thus complement other patient data used in regulatory decision-making and collected via conventional methods such as self-reported questionnaires and patient interviews or other RWD capture tools like EHRs (Almeida et al., 2024; Saczynski et al., 2013).

The COVID-19 pandemic rapidly accelerated the adoption of digital technologies in clinical care for remote care delivery and patient monitoring, and accelerated the digital collection, management and sharing of patient data (Manteghinejad & Javanmard, 2021). The profusion of mHealth data from routine clinical care combined with the proliferation of mHealth solutions for personal health monitoring, have led to a wealth of patient generated data in a post-COVID world (Negreiro, 2021). At the same time, transparency on research studies and decision-making, data quality and reliability, data protection and patient consent have become more important than ever to shape the utility of mHealth data for scientific research (Manteghinejad & Javanmard, 2021).

[1] *Current working definition of RWD (Reflection paper use real-world data non-interventional studies generate real-world evidence* (European Medicines Agency, 2024b)*)*

Since 2020, the joint HMA/EMA BDSG has been driving the transformation towards even more data-driven regulatory decision-making. Their vision on Big Data is a strengthened regulatory system that can efficiently integrate the totality of evidence into its assessment processes to support decision-making (HMA/EMA joint Big Data Steering Group, 2023). Knowing when and how to have confidence in novel technologies and the evidence generated through these will benefit public health by informing and accelerating medicines development, improving treatment outcomes and facilitating earlier and more efficient patient access to new treatments. The 4th workplan of the BDSG was published in July 2023 and intends to investigate in what capacity mHealth data could be useful for regulatory decision-making and to support the implementation of the European Union Medicines Agencies Network Strategy to 2025 (European Medicines Agency, 2020, 2022; HMA/EMA joint Big Data Steering Group, 2023).

3. Methods

A review of literature was conducted between December 2023- January 2024, complemented with an exploratory search of the EMA regulatory pipeline internal data base (see Section 5 for further information).

The literature review was done on Embase given its large library of articles focusing on life sciences, medicine and healthcare. Embase was searched without any time restriction, using a mix of keyword searches and subject heading terms to ensure a maximum coverage of the database. Search terms were developed using the Emtree subject headings. The search terms were applied to the papers' title, abstract, or keywords and the search was filtered for English language publications only. Given the fact that the topic of interest is interdisciplinary, various terms were used to refer to relevant concepts across publications, following an iterative approach. The search terms were refined as the papers were read to include as many possible related themes as possible. Using the final search string, 5589 total search results were obtained, out of which 2737 search results were articles (49%) and the rest were reviews (2852 – 51%). Articles were included if their research focus was evaluating mHealth data or related aspects such as digital endpoints measured from mHealth data for example. Articles were excluded if they did not give relevant information on the utility of mHealth data for regulatory decision-making. A prioritization exercise was conducted on the search results, leaving 82 papers included for the literature review. More information on the detailed search strategy can be found in Annex 10.2.

Additionally, a preliminary review of internal EMA regulatory pipeline data was undertaken to understand if and through which regulatory procedures is the Agency receiving or being consulted on regarding mHealth data. This review took place in February-March 2024 and at least 30 product related submissions or interactions with the regulators were identified to have discussed mHealth tools or data. As the review was not exhaustive, actual number of submissions is expected to be higher. Findings from the review are further discussed in section 5.

4. mHealth in Clinical Trials to support drug development

While not in the scope of this expert review report, the use of mHealth data generated within a clinical trial setting in the context of drug development needs to be acknowledged to provide a comprehensive view of the full potential of mHealth data.

Clinical trials using mHealth data are increasing in number. In fact, the number of studies using connected technologies by 2021 had doubled since 2016 and is growing incrementally (IQVIA, 2021). The Clinical Trials Transformation Initiative (CTTI), a partnership between industry, academics and regulators, is one of the examples of recent investments in this domain aiming to offer a broad suite of recommendations to, among others, guide the successful design and execution of clinical trials using

fit-for-purpose mHealth tools (*Clinical Trials Transformation Initiative - CTTI*, n.d.). A particular focus is placed on the development of novel endpoints representing more accurately the patient experience, as well as a strategy for collecting and sharing mHealth data with regulatory bodies.

Though mHealth data has been receiving more attention in clinical research, challenges linked to patient consent, data privacy and security, data validation and interpretation, technical literacy of trial participants and/or clinicians and maintenance of patient engagement in longer trial periods, exist and may complicate the use of mHealth data in clinical trials (Kakkar et al., 2018). This is in addition to technical challenges inherent to the use of mHealth tools that could affect phones and wearables battery life, participants' internet access and connectivity or different smartphone operating system and updates (Kakkar et al., 2018). These issues are also present in the real-world context and will be discussed as such later in this expert review report (namely in section 8).

Still, the use of mHealth tools in a clinical trial setting provides several benefits for medicines developers, allowing accurate and efficient measurement of digital measures and patient reported outcomes (PROs) while streamlining operational factors like patient consenting and enrolment (Naik et al., 2020). The remote monitoring capabilities of mHealth tools may also reduce geographical limitations of enrolment and data collection, making decentralized and remote trials more viable and cost-efficient while decreasing the logistical burden on patients and researchers (Artusi et al., 2020; Naik et al., 2020).

In this report, digital measures refer to objective quantifiable measures of physiology and/or behaviour collected and measured through digital tools. The term digital endpoint is used to refer to a variable that comprises of digital measures reflecting an outcome of interest in a study to address a specific research question.

5. Current use of mHealth data in the European Medicines Agency regulatory pipeline

The observed increase in the use of mHealth tools in drug development in the last 5 years suggests that the coming years will continue to see a rise in the use of mHealth data in regulatory submissions.

A non-exhaustive internal review in EMA regulatory pipeline internal data base showed that EMA and regulators are being consulted on the use of mHealth data and are receiving submissions from Industry using such data at different steps of the regulatory processes:

- **Early Interaction:** The EMA's Innovation and Development Accelerator, previously known as Innovation Taskforce (ITF), is discussing products that intend to use mobile applications as a part of the treatment plan in the areas of cardiovascular diseases and psychiatry. Other examples include applications for products treating primary hypertension and insomnia which are expected to collect data on prescribed dose and share such patient data with the treating health care professional (HCP) to allow for individual tailoring of treatment by adjusting the dose.
- **Qualification:** The clinical outcome assessment SV95C (the 95th centile of the stride velocity) was the first, and to date the only digital endpoint to receive a qualification opinion by the EMA for which all data was captured using wearable devices (European Medicines Agency, 2023b). Currently, several other digital endpoints and methodologies are undergoing the EMA qualification procedure in the areas of dermatology, neurology, oncology, and cardiovascular disease among others. These include biomarkers and endpoints measured with mHealth tools or analytical approaches for digital data using Artificial intelligence (AI) and Machine Learning (ML) methodologies.

- **Scientific Advice:** several products using mHealth tools in the therapeutic areas of cardiovascular diseases and neurology have sought EMA scientific advice. Among others, applicants are seeking advice on various apps for the collection of real-time patient data and on PRO measures to support MAAs and/or for qualification of the novel methodology.
- **MAA:** EMA and its scientific committees are discussing submissions of products that include mHealth devices or data seeking a marketing authorisation (initial or variation) in the areas of oncology, psychiatry, and endocrinology. Examples of mHealth in these submissions include wearable sensors to collect data on medication use as well as mobile apps to record, track and manage patient data and drug use data.

6. Use cases for mHealth data in regulatory decision-making

Recently, the opportunities offered by RWD to support regulatory assessment of medicinal products have been explored in three main domains: 1) to support planning and validity of marketing authorisation applicant studies, 2) to further understand the clinical context, and 3) to investigate associations and the impact of the medicinal product (European Medicines Agency, 2023c).

When generated as RWD, mHealth data may contribute to the same use cases and provide additional complementary insights to these three domains as discussed in the following sections. Given the novelty of mHealth data use in regulatory decision-making, there are limited examples of actual use of mHealth data by regulatory bodies in decision-making. Yet, drawing on examples of collection and use of mHealth data by health care systems, and patients making use of modern digital devices, the sections below outline how and for which purposes in regulatory decision-making mHealth data may be leveraged.

A summary of the regulatory use cases for mHealth data collected in the real-world is presented in table 1 below.

Table 1. Summary table of potential regulatory use-cases for mHealth data.

Support the planning and validity of applicant studies	Understand clinical context	Investigate associations and impact
Design & Feasibility	***Disease Epidemiology***	***Effectiveness & Safety studies***
Inform Eligibility Criteria • Early stratification based on symptom clustering from app data Guide Recruitment • Choice of study populations and locations from geographical data, remote screening and enrolment of participants Inform choice of Measurements • Choice of meaningful study outcomes using real world PED Make studies more feasible • More robust and efficient remote data collection	Disease Progression • Wearables to measure symptom progression, digital twins to model disease progression Risk Factors • Wearable sensors measuring environmental and lifestyle factors Disease Spread • Apps tracking spread of infectious diseases and prevalence of non-communicable diseases	Signal Detection • Report of safety concerns or side-effects through mHealth apps ADR Characterisation • Wearables and apps can provide detailed insights into the type and severity of ADRs Measuring effectiveness • Wearables and apps can measure physiological biomarkers and other endpoints associated with effectiveness of a medicine, • Cardiovascular function has received particular attention by medical research community
Representativeness & Validity	***Clinical Management***	***Impact of regulatory actions***
Assess external validity & representativeness • Assessment of trial representativeness through data integrated to EHRs and registries	Treatment Patterns • Patient facing apps integrated to national health care systems provide detailed insights into standard of care Medicine Prescription Rates • Apps for HCPs can measure prescribed medicines	Measure ADR rates and severity • Data from mHealth apps and wearables can be analysed to make inferences about changes in ADR rates HCP knowledge & Attitudes on RMMs • Apps could be used to assess HCP knowledge on risk minimisation measures, though evidence is limited
	Drug Utilisation	
	Medication use in Real World • Medicine tracking apps and wearables can monitor actual medication intake Drug use Recurrence • Wearables and apps can identify and measure relapse	

6.1. Support the planning and validity of applicant studies

Design and feasibility of planned studies

mHealth data may help to inform the design and feasibility of both safety and efficacy/effectiveness studies before and after marketing authorisation by generating valuable insights into disease epidemiology and patients' characteristics (see also section 7.2). These use cases can be particularly useful in the evaluation of medicines for special populations, e.g. in the case of the paediatric population where such insights can help inform the feasibility of clinical trials in children or the choice of relevant endpoints.

Insights into disease epidemiology and patient characteristics can guide the definition of eligibility criteria for studies and the recruitment of patients. Data from the MASK-air® app have been used to identify disease profiles of patients with asthma, and to cluster patients based on symptom severity, medication use or treatment response (Bousquet et al., 2023). When a mHealth app is paired with a wearable or other connected data capturing tools, it makes it possible to perform remote early stratification of patients into different groups. Additionally, apps and smartphones have the ability to collect individual level location data using Bluetooth and GPS technology to improve understanding of geographical prevalence of patients but also identify where and in which populations mHealth tools are

already extensively used (Wirth et al., 2020). These insights can subsequently help decide in which populations and study locations remote patient monitoring could be feasible (Wirth et al., 2020). The AllerSearch hay fever research showed how mHealth apps have streamlined the recruitment of patient by enabling remote online screening and allowing participants to enrol and give informed consent for study participation directly upon downloading an application from an app store, making large scale recruitment of patients from various regions more feasible (Inomata et al., 2022).

Another utility of mHealth data in this area is to inform the choice of measurements and outcomes that reflect more accurately what is observed in the routine care and experienced by patients in daily life. Through capturing patient experience data (PED), mHealth data may be used to inform which outcomes considered as possible study endpoints are most relevant from the patient's perspective (Kluetz et al., 2018; Lobach et al., 2022). For example, mHealth apps have been used in various studies, in clinical trials as well as studies investigating routine clinical care, to collect PROs such as impact of treatment on quality of life (QoL), as both primary and secondary study endpoints (Sarbaz et al., 2022; Shelton et al., 2021). In other instances, smartwatches have been used to objectively measure physiological endpoints such as heart rate variability or walking capacity in the real-world (Ding et al., 2023; Rens et al., 2021). Equally, by capturing the patient experience, mHealth data have helped to develop and define meaningful endpoints for patients. For example a certain level of change from baseline in walking capacity could be considered meaningful for patients when it has a positive impact on the their quality of life (Manta et al., 2020). Measuring endpoints like walking speed at home is less burdensome than travelling to a study site, especially for patients with impaired mobility, and it provides outcomes measurements that are more representative of the patients real-world experience (Aryal et al., 2023). Real-world measurements like these can in turn inform decision-making on relevant endpoints to be considered for safety and efficacy studies.

mhealth data collection using mHealth tools also tends to be more cost effective than using conventional disease screening tools such as ECGs and may increase study feasibility (Geldsetzer et al., 2022). mHealth tools have been found to increase study retention, allowing for more complete reporting of study outcomes (Fonseka & Woo, 2021).

Finally, efficient and continuous collection of patient data may reduce the need for large sample sizes and allow for adaptive trial decisions to be made rapidly when necessary.

Representativeness and validity of completed studies

mHealth data may provide useful information to support the assessment of the representativeness and validity of applicant studies. In this context, regulators are already leveraging EHRs, claims databases and registries in RWD studies to inform the evaluation of the external validity of an applicant study by measuring the representativeness of the clinical trial (CT) population vs. the real-world target population (European Medicines Agency, 2023). mHealth data could further expand the possibilities and the granularity of such RWD studies.

In one example, data from an mHealth application and connected wearable devices were directly integrated into EHRs through on-device data sharing, allowing patients to record asthma symptoms within their EHR (Genes et al., 2018). Some companies, such as Fitbit, have made specific agreements with EHR systems, like Epic, to enable direct integration of patient wearable data to EHRs (Muzny et al., 2020). Beyond EHRs, mHealth connected patient registries gathering wearable and smartphone data in addition to PROs widen the possibilities for RWD studies (Webber et al., 2023). This is the case for the ArthritisPower registry for patients with musculoskeletal and rheumatic conditions or the Fox Insight registry for patients with neurodegenerative conditions such as Parkinsons.

6.2. Understand the clinical context

As demonstrated by several use cases in the report on the real-world evidence framework to support EU regulatory decision-making, understanding the clinical context is critical for any type of regulatory evaluation procedure (European Medicines Agency, 2023c). Tapping into the opportunities offered by mHealth data to increase insights in this area would therefore benefit all regulatory stakeholders and beyond.

Support the understanding of disease epidemiology

mHealth data can aid in facilitating a better understanding of the natural course of various diseases, as well as in identifying the timing and incidence of different symptoms across diverse populations.

Thanks to the large array of sensors in currently available devices, mHealth data are collected across a large variety of therapeutic areas to measure disease progression and physiological measures, as seen in table 2 (Annex 10.2.).

Continuous generation of mHealth data from wearables give longitudinal insights into multiple disease parameters at once, enabling to better understand disease progression. Consumer-grade wearables have already been used to gather data on changes in various physiological systems during COVID-19 infection (Mayer et al., 2022). Data from wearables are being used to construct detailed digital twins to model disease progression, with most research focusing on modelling cardiovascular disease and various cancers (Xames & Topcu, 2024). In these two examples, mHealth data may support epidemiological research and be used to model treatment effectiveness in patients or as digital controls in studies to compare with observed effectiveness and safety of a treatment (Armeni et al., 2022; Sheng et al., 2023; Steinhubl et al., 2024).

mHealth data can also be used to identify and measure physiological, lifestyle and environmental characteristics and risk factors for a disease or disease events through various means such as PROs, vital signs monitoring or environment monitoring (Cruz-Ramos et al., 2022; Park et al., 2022). Using a wrist worn consumer wearable, it was possible to collect data on humidity, ozone, temperature and activity levels to measure known asthma symptom triggers (Mallires et al., 2019). These data are useful for considering potential risk groups and contextualizing the use of a medicinal product and its side effects within the various contexts patients live in.

On a population level, mHealth apps are allowing for the tracking of the spread of diseases, as seen with the COVID-19 infection tracker apps that used Bluetooth and GPS technology to identify location and contacts of infected individuals. In March 2020, ZOE launched in the UK a COVID symptom tracker app to rapidly advance research on COVID-19. In just a week, one million people downloaded the app. In fact, spatial and temporal trends identified from mHealth data collected through several infectious disease tracking apps were found to match those collected from traditional disease surveillance methods (Pandit et al., 2022). These data can be especially useful in post authorisation monitoring to understand the spread of disease while getting insights on the large-scale impact of approved medicines in that disease area. The uses are not limited to infectious diseases, several mHealth apps exist and are in use to measure and monitor prevalence of non-communicable diseases, which can give important insights into identifying disease clusters and possible unmet needs in current care (Geldsetzer et al., 2022). mHealth data in here is ought to be viewed as a warning sign to trigger a larger exploration of the unmet need.

Clinical management

mHealth data may be used to better understand the actual clinical standards of care across countries, e.g. difference in patient treatments, differences in the clinical care for the same disease across different populations and regions, or difference in drug prescription patterns. It is important to

understand how patients are currently being treated and to measure unmet needs in current clinical care to anticipate what benefit the authorisation of new medicines will bring.

Several health care systems in Europe have integrated mHealth technologies which capture patient medical histories in detail. In the UK, patients can view and manage their medical records, appointment history and renew/update their medicine prescriptions via a central digital platform like the National Health Service Application (NHS App). Other countries, like the Netherlands, have separate digital platforms for a patient's general practitioner and hospital data and use additional platforms, mostly mobile applications, for combining all of the patient information known as a personal digital healthcare environment ("persoonlijke gezondheidsomgeving" (PGO)) (Zaken, 2016). Some PGOs, like the SelfCare app, allow patients to link their wearables and other health applications to the PGO to combine their medical records and medicine prescriptions with data generated by patients (*Selfcare – Persoonlijke Gezondheidsomgeving (PGO) – Take Good Care of Yourself*, n.d.). When used to the full extent, the data on PGO applications represent the most complete picture of a patient health status and history inclusive of the clinical care received, the medicines prescribed and their actual use, as well as physiological data to measure disease progression, adverse events or quality of life. In these ways mHealth data can merge insights from clinical care and patients' daily life to a level of detail not available through other RWD sources and thus could be used to understand not only treatment patterns and clinical care approaches but also their impact on patients daily functioning.

Alternatively, mHealth tools can be employed to gain direct insights from HCPs on clinical management. A mHealth app created for anaesthesiologists was used to collect information on prescription rates of Sugammadex, enabling the possibility to study global clinical practice patterns through the acquired mHealth data (O'Reilly-Shah et al., 2017).

Drug utilisation

mHealth apps and wearables offer a unique utility in collecting additional data to further understand drug use in different populations in a real-world context. Such data can support regulatory discussions during scientific advice procedures or help detect potential issues in the current use of certain medicines as well as help inform possible measures to address these issues. Some examples have been given in the report presenting the real-world evidence framework to support EU regulatory decision-making (European Medicines Agency, 2023c).

Medication tracking apps like Pillo and MedicineWise allow patients to track aspects like duration of drug regimen and dosage for several medicines at once while facilitating adherence through reminders and notifications (*MedicineWise App*, 2020; *Pillo*, n.d.). MedicineWise also lets patients track symptoms and ADRs and share their data directly with their HCP, opening a broader avenue for the incorporation of drug utilisation data for regulatory use (*MedicineWise App*, 2020).

Similarly, wearable devices can be used to track medication intake. A smartwatch combined with an mHealth app was used to demonstrate the feasibility and usability of a wearable device to remotely assess medication adherence and monitor mobility in people with mild-to-moderate Parkinson's disease (Debelle et al., 2023). The watch provided feature to record the dosage, the number of units taken, and the time the medication was taken.

mHealth tools have also been used to predict drug use recurrence, where data from wearables and an mHealth app were used to identify and measure biomarkers associated with relapse (Mahoney et al., 2023). As such, mHealth data can be useful in the development and assessment of therapies for substance use disorders (SUDs). Such insights would be helpful for regulators to contextualise the clinical use of currently available treatments for various disease.

6.3. Investigate associations and impact

Such use cases can be particularly useful for the PRAC when evaluating safety signals, providing additional insights to help contextualise for example to a drug or a class of drugs, or to certain subgroups of the treated population.

Effectiveness and safety studies

mHealth data may enhance studies on the safety of a medicinal product as part of pharmacovigilance related activities, and those on effectiveness for example through the monitoring of biomarkers associated with a medicine.

mHealth devices have been used to collect data on novel, severe or recurring ADRs, which could highlight safety concerns for a medicinal product. mHealth apps specifically are advantageous for reporting of patient reported ADR as most patients tend to prefer to report ADRs using an mHealth app over web-based applications or paper surveys (Wilson et al., 2016). This is likely to result in more complete and informative data for safety studies (Wilson et al., 2016). Several ADR reporting apps such as the MedWatcher or YellowCard are already in use in countries in Europe and globally for pharmacovigilance, and present advantages for rapid and simple reporting, collection of structured data and reduction of risk of missing data by identifying mandatory data entry fields for example (Parracha et al., 2023). In 2020, EMA launched an early safety study on COVID-19 Vaccines and collected PRO data from patients via mobile apps (EUPAS39798) (European Medicines Agency, 2023c). Several studies have leveraged smartwatch data from patients in registries such as ArthritisPower for real-world evaluations of safety and efficacy of medicinal products.(Harrold et al., 2023; Nowell et al., 2022).

mHealth apps can be equally beneficial for collecting physician reported ADRs. The use of an in-app survey facilitated a global assessment of anaesthesia providers and demonstrated useful applications in monitoring adverse events and estimating their rates in routine clinical care (Jabaley et al., 2018). The expert knowledge of physicians is likely to provide more accurate and reliable ADRs, while the easy-to-use and efficient data collection method via the app may increase physician ADR reporting rates.

mHealth data may also contribute to inform on the effectiveness of the medicine in patients in a real-world context. Apps such as the Cara Care app for irritable bowel syndrome (IBS), one of the fully certified mHealth apps included in the German healthcare reimbursement scheme, collects data on outcomes such as gut symptoms, mood, while also tracking lifestyle factors like meals and physical activity (*Cara Care für Reizdarm*, n.d.). Used in a pilot effectiveness study for a peptide supplement, this app collected data for the primary study endpoints and changes in different IBS symptoms from baseline, thereby helping to inform how effective the treatment was (Abrahams et al., 2022).

The use of mHealth tools to assess cardiovascular function has also gained more research focus over the years and led to significant developments in consumer wearable technology. Smartwatches from Apple and Samsung among others have been used in several clinical trials and some have gained regulatory approval for identifying and measuring Atrial Fibrillation, while other studies have shown they can also accurately detect other type of arrythmias (Babar et al., 2023; Pay et al., 2023). Since smartwatches are widely used, they may be a useful data source for real-world monitoring of treatment outcomes or side effects of therapies which impact cardiovascular function.

Impact of regulatory actions

The use of mHealth data for measuring the impact of regulatory actions is limited, although changes in rates of ADR occurrence and severity pre to post authorization derived from mHealth data may be used to describe the impact of ADR minimizing measures. Alternatively, mHealth tools may be used in the evaluation of HCP knowledge or attitudes about risk minimization measures (RMMs) by conducting

surveys through mHealth apps, however this would only be useful through centralized apps instead of a different one for each product.

7. Challenges and opportunities to use mHealth data in regulatory decision-making

mHealth data need to meet sufficient regulatory requirements, as do other types of RWD. mHealth data should be of high quality (in particular regarding relevance and reliability in line with EMA's Data Quality Framework (DQF) (Data Analytics and Methods Task Force, 2023)), accessible, interpretable, collected timely, ensuring patient privacy and complying with data protection requirement, and analysed using appropriate and robust epidemiological and statistical methods.

This report chooses to highlight the most commonly reported characteristics of mHealth data, as per the following:

- mHealth data accumulate rapidly in large datasets with mostly continuous numerical data. Much of the continuous data is unlabelled e.g. heart rate data collected from a smartwatch often requires additional steps to label anomalies vs. normal heartbeat before processing. Free text data entry especially through mHealth apps is also possible but may present issues such as spelling errors for medication names. Quality and completeness of the data may vary depending on multiple factors such as the type of tool and how well validated the tool and its measurements are, the accuracy and placement of the sensor, the data collection setting, and the patient motivation and technical literacy to input data.
- Data is collected directly from the users (passive data collection through wearables or smartphone sensors or active user input).
- Data protection varies depending on the mHealth device. Though GDPR applies to all mHealth data, the developers knowledge of data protection requirements and the medical device status of a device, which determines whether the Medical Device Regulation (MDR) must be abided to, are amongst other factors that may create large disparities between mHealth data from different sources (van der Storm et al., 2023). As a result, transparency in data management varies, and given the complexity of the mHealth ecosystem, issues in data governance may arise as the roles and responsibilities may be difficult to trace.
- mHealth data capture diverse patient information, such as demographic data and physiological measurements, PED including PROs and health related quality of life (HRQoL), behaviour and geographic information.
- Access to mHealth data, especially granular raw data depends on private companies' willingness to grant the access. Some mHealth data may also be accessible through registries and EHRs data sources.

Further information on characteristics of mHealth data sources can be found in Annex 10.4.

Considering the characteristics of mHealth data, their challenges and opportunities when used to support regulatory decision-making are discussed in this section. These are structured around the three pillars of the OPTIMAL framework for RWE published in 2019 by EMA: operational, technical and methodological (Cave et al., 2019).

7.1. Operational challenges and opportunities

Operational challenges include governance, access to data and the regulatory landscape around mHealth data, as shown in table 3 (annex 9.3.).

Data protection regulations in the EU govern access to patient health data to protect the data subject, i.e. the patient (Carmi et al., 2023). Importantly, several freely available mHealth apps were found to not include proper declaration of privacy policy or explicit user consent for personal data collection, sharing, or secondary use, yet data are still shared with third parties (Alfawzan et al., 2022).

Correct implementation of data protection and transparency measures in line with the GDPR, specifically related to de-identification of patient data and to the request for patient consent for data sharing, storage and reuse, is essential for the use of mHealth data for regulatory purposes. In certain instances, patient consent might be waived, e.g. when pseudonymised or anonymised patient data is used for health research. Recent reviews have showed that patients generally support sharing personal health data for secondary use that benefit the public rather than for commercial gain (Baines et al., 2024; Kalkman et al., 2022).

Access to mHealth data generated by consumer apps and wearables might not be as easy for regulatory use as compared to access to mHealth data controlled by patient registries or health care institutions, where the rules and safeguards on patient data protection are designed in line with GDPR.

Several logistical aspects can also affect access to mHealth data. Where and in what format mHealth data is stored is central to its accessibility and utility. Data may be stored locally on the user's device, in the cloud or on a company's or health institution's servers for example, thus resulting in a fragmented data landscape. Data may also be stored in a variety of formats and structures. This not only creates challenges in locating the relevant data, but also accessing it given the different parties controlling and holding the data. However, with developments in connective technology and data sharing architecture, access to mHealth data is becoming increasingly easier. Most recent smartphones allow patients to link their wearable data to a health management app, such as Apple Health and Samsung Health, which can further be linked with EHRs. In the UK, for example, the hospital mHealth app MyCARE is used for patient management at the Milton Keynes University Hospital (MKUH) and has the infrastructure and access to link patient data, such as activity, heart and sleep measurements from the mobile phone health app to the hospital and patient records (NHS, n.d., 2022). Wearable devices now can even access the internet using Bluetooth 4.2. overcoming the need for an associated smartphone and allowing direct linkage with the patient's EHR (Davis et al., 2016), which in turn enables more reliable and complete passive clinical real-world data collection.

The European Health Data Space (EHDS) as a key initiative creating a common health data ecosystem in Europe is expected to expand access and availability of mHealth data (European Commission, 2022a). It builds further on the Data Act for example as another enabler for better and more secure access to a wide range of health data (European Commission, 2022a). Leveraging the EHDS outcomes and framework is a significant opportunity for more access to reliable and high quality mHealth data for medicine regulation.

Alternatively, actions can be taken to facilitate access to mHealth data directly from the patients. Initiatives like the All of Us research program in the US gather patient data including (raw) data from wearables from a diverse population for health research and create a large and structured database for which patients knowingly share their data (Master et al., 2023). A significant opportunity remains in advancing health research and supporting evidence generation for EU medicine regulation by fostering access to a similar health database reflective of the diversity of the European patient population.

Finally, depending on the intended use of a mHealth device, different regulatory pathways and legal obligations guide their development and use. Consumer wearables, mobile devices and lifestyle apps are developed for various purposes, often not primarily for the collection of research grade clinical data which put them outside the scope of regulatory assessment. Not only might this impact their data quality but the differences in certification, data protection measures and patient consent might create barriers for their use in regulatory decision-making. But this review showed how some consumer

mHealth tools have already been used for medical data collection, indicating that opportunities exist in leveraging these tools to generate appropriate and reliable data for selected regulatory use cases. Moreover, opportunities exist in increasing regulatory acceptability of mHealth data through regulatory mechanisms such as scientific advice and qualification of digital measures agnostic to device.

7.2. Technical challenges and opportunities

For regulatory decision-making, data quality (i.e. completeness, and reliability) and interoperability are one of the main challenges for the use of mHealth data.

Various factors can indeed restrict the data quality of mHealth data when generated in a real-world setting. Short battery life of mHealth tools or patient lifestyle and behaviour may impact the completeness of data. Smartphones require sufficient storage and battery to run mHealth applications and interact with wearables while these activities themselves will drain battery quickly and use up large amounts of the devices working memory. A fit too lose may lead to missing or inaccurate data from smartwatches. Depending on the tool, sensors may work differently in environments of different humidity or temperature, or differently by skin type, as some watches using photoplethysmography (PPG) have been found to work differently based on skin tone (Lima et al., 2022). Additionally, patients may have varying levels of knowledge and skills for correct data collection, thus data collection methods relying on more active user participation may be less desirable for some populations. All these factors can lead to incomplete and/or incorrect data capturing.

On the other hand, leveraging the data collection and data management capabilities of a combination of wearables, mHealth apps and smartphones can help fill in the gaps of the missing data, while passive data collection tools can provide important real-world insights without the need for user input.

Several of the currently available wearable tools have been shown to be extremely accurate in measuring health relevant factors. Various regulatory bodies have even certified some consumer grade devices for medical uses. One example is the Food and Drug Administration (FDA) in the US which certified features on the Apple Watch and the Fitbit Sense smartwatches for atrial fibrillation detection rendering them a class 2 medical devices (Lima et al., 2022). In Europe the features have received CE certification.

Despite several challenges impacting the quality of mHealth data, identifying the most accurate tools and combining several data sources for a holistic approach offer the opportunity to increase the value of mHealth data for regulatory decision making.

The interoperability of mHealth data is often limited by insufficient data exchange standards (Lobach et al., 2022), but several mHealth data sharing approaches exist (e.g. data being shared directly from sensor or a cloud or an intermediate system such as a smartphone) (De Arriba-Pérez et al., 2016). The multiplicity of approaches employed by different mHealth device developers restricts interoperability and poses a challenge for the use of mHealth data (De Arriba-Pérez et al., 2016).

Opportunities exist for the harmonisation of approaches or development of new platforms for efficient mHealth data sharing, while novel technological solutions may also help overcome the challenges in other ways. Recent developments in AI and ML technology have demonstrated possibilities for more efficient processing and analysis of large, complex, and even incomplete data. (Frid et al., 2022) successfully linked mHealth app data with an EHR system by using AI to structure the patient data and making it interoperable for linkage with the health record database. (Huang et al., 2022) show how AI approaches have been used on several occasions on heart data from wearables for data processing and analysis and to identify signals of a heartbeat from continuous heart data. As such, AI has already been used to tackle technical challenges related to mHealth data and the next years are likely to see more developed and widespread applications of AI on mHealth data, enhancing its utility.

7.3. Methodological challenges and opportunities

In addition to operational and technical considerations, methodological issues must be considered when evaluating the use of mHealth data for regulatory decision-making. The choice of relevant and fit-for-purpose digital endpoints, combined with the use of appropriate study designs and data collection tools with robust analytical methods, are necessary to realise the value of mHealth data.

Given the characteristics of mHealth data previously discussed, conventional methods may not be appropriate for the collection and analysis of mHealth data, and the design of any study leveraging mHealth data must appropriately account for these characteristics and limitations. For example, there may be differences in the accuracy and availability of sensors across device types as well as brands for a specific type of device. Moreover, different device operating systems may allow the same mobile applications to access different device features and thus can lead to differences in the collected data. These differences must be accounted for, so that the data to be collected with the planned mHealth devices in fact addresses the research question at hand despite differences in operating systems for example. Any shortcomings could impact the utility of mHealth data in regulatory decision making.

The sensor technology of many mHealth tools is advanced and provides more and more accurate measurements, however analyses using mHealth data can still fall prey to biases and confounders as not every patient uses such tools in the same way. Relying solely on one single type of mHealth data, such as step counts or other physical activity measures taken with a smartphone for example, is not a reliable and comprehensive measure of an individual's physical activity as users likely do not carry their phone on them all the time, or the measurement may be inexact if the smartphone is carried inside a bag for example. Instead, as wearables have been found to be more accurate for human activity recognition, combining data from smartphones and a wearable or several wearables will allow for more complete and reliable measurements (Piccinini et al., 2020).

Data from a particular mHealth tool has been suggested to offer even greater potential when combined with data from another tool, medical device, or method of active data collection (Almeida et al., 2024). A recent systematic review exploring the reliability and validity of commercially available wearable devices found that most consumer-grade wearables accurately measure heart rate and steps for example (Fuller et al., 2020). The review also concluded that reliability of measurements across different devices and brands is very strong, though more studies on reliability aspects are needed. As such, the currently available wearable devices in general seem to be reliable and thus should provide similar results when measuring a particular concept of interest. In other words, if the passive physical activity measurements of two consumer grade mHealth devices of a single patient are aligned, they are both more likely to be accurate and can serve for mutual validation. By extension, intermittent mHealth data can also be validated with another mHealth tool, for example by cross-checking the data entries from a medicine tracking app with the movement and physiological measurements of a smartwatch to check for ingestion and onset of effect of the medicinal product. In addition to such cross-validation utility, mHealth data can bring added analytical value through augmenting study measures by helping construct composite endpoints for example (Goldsack et al., 2021).

As such, mHealth tools can be leveraged to provide a detailed and holistic assessment of the patient's state giving direct insights on the extent to which a medicinal product is creating meaningful change in patients' daily life. Consequently, it is precisely the direct access to the patient experience that sits at the core of the utility of mHealth data for regulatory decision making.

While mHealth tools allow the collection of important digital endpoints in real-world settings, efforts to continuously support the development and validation of endpoints derived from mHealth data and their clinical relevance and accuracy will enable their acceptance at large. There is a notable opportunity in advancing the work towards accepting more digital endpoints agnostic to a data collection device.

Continuous and passive data collection is one of the major strengths of mHealth tools for RWD collection. The breadth and precision to measuring the real-world patient experience that mHealth data brings while allowing for user friendly and wireless data collection is unparallelled by conventionally collected data. Because of these characteristics mHealth data has a specific opportunity for use in research, especially in some specific patient populations such as paediatric populations. The 6-minute walking test (6MWT) is a widely used metric to assess functional capacity and disease progression but the measurement may not be accurate and the test can be difficult to conduct in children with chronic or cardiac issues for example (Bartels et al., 2013). Wearables taking passive measurements during daily moderate activity can be an accurate predictor of the 6MWT results and could be used as a surrogate (Schubert et al., 2020). Wearables have also been used to measure outcomes for gait and physical activity, and can do so in various forms, such as through a smart shoe (Hegde et al., 2017; Junior et al., 2020). As such, accurate, user friendly and passive data collection methods would be helpful in measuring walking capacity in children for example.

Generational and cultural differences in the use of mHealth apps and differential levels of access to digital devices in different regions may lead to differential and biased representation of a population for a given condition. Younger, employed and more highly educated populations are more likely to own and use digital devices leading to unequal data coverage of the patients and representativeness issues (Shandhi et al., 2024). But considering the development of interoperable and adaptable digital tools and the increasing use of mHealth devices, some issues around over or underrepresentation might be addressed in the future.

As mHealth data falls in the realm of big data, appropriate data processing and analysis tools must be employed to make meaning of mHealth data. AI approaches have been used for the analysis of various mHealth data, for example to analyse heart rate variability from wearable data. Spathis et al. (2019) developed a deep neural network (DNN) model to analyse heart rate from smartwatch data. The AI model in this case made the analysis especially helpful by allowing to generate meaningful representations of heart rates from a large set of unlabelled data. Moreover, (Haugg et al., 2022) describe ML approaches for blood pressure measurement using data from a smartphone, and how several recently developed ML methods using both regression and classification models have a level of accuracy that is within the clinically acceptable range. In another recent example, ML was leveraged to analyse data from a wearable and mobile app to assess patient symptoms and determine the patient's recovery status (Leitner et al., 2023). Combining such data with mHealth data on patients' medication intake could be useful for assessing the effectiveness of a medicinal product in the real world.

8. Points for consideration for future action

Despite the challenges highlighted above, mHealth tools are already being used to collect data which could be leveraged to support regulatory decision-making with many more opportunities waiting to be explored. mHealth data seems to be especially useful for informing the planning and evaluation of studies, and in providing supporting evidence for evaluation of the safety and effectiveness of medicines in the real world. While the reliability and accuracy of mHealth data may vary and remains a challenge, the unparalleled direct reflection of the daily patient experience together with the ability to provide continuous RWD data reflects its utility for EMA's regulatory decision-making processes. As such, the following points for consideration for future actions, also summarized in Table 4 (Annex 10.2) are being proposed to foster their use and establish their value in regulatory decision-making.

8.1. Operational points for consideration for future actions

1. Leverage work on patient experience data and expedite access to mHealth data

mHealth data is closely linked with patient experience data (PED) as mHealth tools allow insights into patient experiences to an unparallelled level of detail. As such it is recommended that further work on PED should explore how mHealth data can be instrumental in the context of PED. To systematically include PED in medicines development and regulation, the EU network is currently developing a reflection paper on the best EU approach to define, generate, collect and analyse PED. It would be important to build on the ongoing work and initiatives around PED to provide further clarity on how to enable the use and establish the value of mHealth data for regulatory decision-making.

Before mHealth data can be adopted for routine decision-making processes, better access to it must be facilitated. Some mHealth data can be accessed through already established RWD pathways. Recent advancements in interoperability and data sharing architecture have indeed allowed for mHealth data to be directly shared with EHRs, some patient organisations' dedicated platforms, as well as disease registries. Alternatively, mHealth data can be accessed directly by regulators from private companies which make these data available specifically for health research.

However, a more ambitious point for consideration for future action would be for the EU regulatory system and network to proactively and adequately access mHealth data directly from patients. Some initiatives, such as the German Corona Data Donation Project have collected patient mHealth data in Europe from volunteers, though the resulting database is often limited to specific condition (Gilbert et al., 2024). Others such as the ZOE Health Study, have seen its uptake continuously increased and have been used to support epidemiological research.

Instead, a large European health database could be launched where patients from all around Europe regardless of disease or treatment status can choose to share their data directly in a common platform. This would allow for unprecedented opportunities for the EU regulatory network as well as for health researchers in Europe to patient data and anchor these at the heart of medicines development and regulation. With particular consideration and focus on PED and patient generated mHealth data, this could greatly complement other significant initiatives in the European health data landscape such as the EHDS and Data Saves Lives initiatives (European Commission, 2022a; *What Is DataSavesLives*, n.d.). This might be particularly beneficial to collect data from special populations, e.g. in an orphan setting.

As such, a common European patient data platform would create significant opportunities such as:

- Offering a secure platform grounded in consent for patients willing to share their data to support health research. Patients should have the opportunity to decide which uses their data is shared for and stop sharing their data at any point. Continuous data sharing should be incentivised through user engagement and disseminating study results for example.
- Provide an EU level common tool that goes beyond borders and allows to reflect the diversity of the EU populations, creating the possibility for more patterns to emerge as the amount of data grows.
- Provide a sustainable and long-term mechanism to support the EU regulatory system efforts to systematically include PED in medicines development and regulation.
- Keep data secure and personal information private in a common platform. Benefiting from the latest technological progress, patients could share data collected using mHealth tools or other wearable technologies directly from their mobile devices.
- Ensure high quality and standardised data for the generation of evidence, thus helping regulators create robust evidence from mHealth data. Furthermore, gathering a wide array of mHealth data will help define the evidentiary requirements for acceptability of such data across the full range of regulatory use-cases.

- Facilitate engagement and collaboration with patients' organisations.
- Bring benefits directly back to patients as data donors. Patients could be able to see the treatment plans and effectiveness of other patients with a similar profile while patient organisations should be able to interrogate the shared data for relevant research questions for example.
- Expand health research possibilities with mHealth data. By granting access to researchers and thus facilitating further studies on a variety of topics, such Europe wide platform would greatly increase the utility of mHealth data in better understanding disease, treatments, and supporting EU medicine regulation.

2. Increase discoverability of data sources and studies using mHealth data

Leveraging the recent launch of the HMA-EMA catalogues of real-world data sources and studies in 2024, it is now possible to record the data source type for a RWD study as 'Data from digital health wearables' (HMA / EMA, n.d.). To also allow discoverability of RWD sources, the RWD sources catalogues should be updated as well to capture when data have been collected via mHealth tools. Promoting the use of these catalogues in this context will help regulators, as well as other researchers, identify the most suitable data sources collecting mHealth data to address specific research questions, support the assessment of study protocols and results, promote transparency, encourage the use of good practices and ultimately build trust in research based on mHealth data.

3. Ensure compliance with data protection and ethical use of mHealth data

EU data protection legislation is compatible with the secondary use of healthcare data for justified public health and research purposes. Awareness on data privacy, consent and compliance with data protection is crucial for the use and integration of mHealth data into regulation decision-making. EU regulators should engage more with developers and providers of mHealth tools and actors of the medicine regulatory system, to ensure regulatory requirements for the use of mHealth data are understood and data protection is delivered by design. Guidance on interpretation of European data protection legislation might be needed in the context of the use of mHealth data and communication between all the relevant actors will be required. The use of mHealth data, specifically data not developed originally for research or regulatory purposes, must be extensively considered from an ethical point of view for all planned uses for which the extent of patient consent should be critically evaluated. Importantly, implementation of the AI act must be monitored to ensure legal and ethical use of mHealth data generated with the help of AI approaches.

4. Engage and collaborate with all actors and relevant initiatives in the healthcare sector

The effective use of mHealth data to support regulatory decision-making requires a multistakeholder approach:

- Collaboration with the pharmaceutical industry is essential as several regulatory submissions are already using mHealth technologies.
- Public-private partnerships such as the Innovative Health Initiative (IHI) should continue to be leveraged for such multi-stakeholder collaboration on the use of mHealth data (EC, EFPIA, n.d.).
- The EU network should strategically be involved in selected initiatives for understanding their relevance for regulatory decision-making. As such, a list of ongoing EU and international initiatives on mHealth data and tools should be established. Table 5 (Annex 10.5) provides a non-exhaustive list of initiatives to be seen as a starting point relevant for realizing the utility

of mHealth data in regulatory uses. An example is the EU-funded Label2Enable project which will leverage the ISO 82304-2 Technical Specification and its health app quality label to create an EU assessment and EU mHealth label (European Commission, 2022b).

- Early interaction with regulators through the variety of mechanisms available to innovation, such as the Innovation Task Force (ITF) briefing meetings and Scientific Advice, should be further promoted (*Supporting Innovation | European Medicines Agency*, n.d.).
- To develop validated digital endpoints and thus reliable mHealth studies, more precompetitive collaboration should be supported where developers can share expertise, research methods, study outcomes and learnings.
- Additional benefits and use cases for mHealth data might emerge and the needs of downstream stakeholders such as HTA bodies and payers should also be considered in the actions that will be launched.
- Learning from other regulators, sharing knowledge and guidance should be fostered, possibly under the umbrella of International Coalition of Medicines Regulatory Authorities (ICMRA) or via a dedicated workshop to discuss the state-of-the art use of mHealth data in drug development and authorisation.

A multi-stakeholder workshop on mHealth data bringing together the expertise and experience of all the above-mentioned relevant parties should be organised. Such a workshop could discuss the outputs of the current report between stakeholders and agree and define the EMRN vision for the next 5 years regarding mHealth data. Topics could include discussions on the methodological and statistical challenges and opportunities associated with use of mHealth data and how it can help sometimes limited data quality and accessibility.

8.2. Technical points for consideration for future actions

1. Engage with EU and international standards for mHealth data

For mHealth data to be effectively integrated into regulatory decision-making, given the novelty of this data type, requirements should be defined and consider data quality, including accuracy, reliability and relevance (i.e. for which types of regulatory research questions) as well as privacy measures. While common data quality elements in the EU DQF apply to mHealth data as a sub-type of RWD, mHealth data are out-of-scope of the current DQF chapter on RWD (Data Analytics and Methods Task Force, 2023). No clear regulatory guidance in the EU is yet available to evaluate quality of mHealth data and it is recommended to consider developing a specific chapter on mHealth data quality in the near future. Moreover, steps should be taken towards internationally accepted standards for mHealth data use as RWD in medicine regulation. For the time being generic standards such as the widely accepted should continue to be supported by EU regulators Where available, standards specific to mHealth data, for example the IEEE Standard for Open Mobile Health Data—Representation of Metadata, Sleep, and Physical Activity Measures should be promoted (IEEE, 2021). The European Medicines Regulatory Network Data Standardisation Strategy should also be reviewed to consider international standards being developed for mHealth (EMA / HMA, 2021).

8.3. Methodological points for consideration for future actions

1. Increase the understanding and tracking of the use of mHealth data in EU Medicine Regulation

While this review highlights how the potential of mHealth data may be leveraged, more extensive and detailed investigation into the current use of mHealth in the European regulatory space is warranted. Similar to the work done by Bakker et al. (2022) for RWE use in previous MAAs, a strategic initiative should be launched to gather learnings on the use and submission of mHealth data to regulators, both

from MAAs as well as documents from early interactions like SA, from which lessons could be publicly shared and future guidance drafted. Similarly, an analysis of ongoing initiatives on mHealth data could investigate gaps and research priorities and inform the next revision of the EMA regulatory science research needs (European Medicines Agency, 2021).

2. Support the development of mHealth derived measures to meet regulatory standards

EMA published resources include the question-and-answer document on Qualification of digital technology-based methodologies to support approval of medicinal products (EMA/219860/2020), as well as a guidance on computerized systems and electronic data in clinical trials (EMA/INS/GCP/112288/2023) (European Medicines Agency, n.d., 2023a).

More regulatory-qualified digital endpoints measured with mHealth tools, like the SV95C, could be developed in the future. For this to be feasible, regulators should provide their expertise to determine the clinical relevance of mHealth measures through early interactions using regulatory processes such as SA at EMA or through national innovations offices of NCAs. Findings from initiatives which advance the understanding of the reliability and accuracy of mHealth tools should also be leveraged. An example is the MOBILISE–D project working on developing, testing and validating digital endpoints for real world measurements across diseases like Parkinson's and multiple sclerosis (IMI Innovative Medicines Initiative, 2019). Having received a letter of support from the EMA (EMA/234828/2020), their goal is to gain regulatory qualification for a digital endpoint for mobility.

In addition, qualification of the context of use of approved digital endpoints should be considered to be expanded beyond a specific device or disease indication.

For seamless development and use of mHealth data and data sources, it is crucial to ensure that stakeholders in the interface of the MDR and pharmaceutical legislation can interact and work in a complementary way. As more and more applications include the use of a digital tool such as an app associated with a medicinal product, there should be consideration of the feasibility of joint SA, either parallel or integrated, for medicinal products and medical devices (Stephenson et al., 2020). This could allow more successful development of reliable mHealth tools and collection of regulatorily accepted data to ultimately speed up drug development and the regulatory assessment. EMA has set up a focus group (EMA/554023/2023, p.5) which explored what kind of scientific questions would benefit from being addressed in comprehensive discussions on evidence planning in a multi-stakeholder setting, and who would be the required decision makers and experts for such multi-disciplinary discussions (European Medicines Agency, 2024a). The results will be published in a scientific publication.

9. Annexes

9.1. Search strategy and characteristics of the search results

Relevant articles related to mHealth data in medicine regulation were searched in addition to reviewing relevant reviews to ensure mature and reliable findings to answer the research questions. Of the 5589 search results on Embase, 2737 were articles and the rest were reviews (2852). Additionally, keyword searching was used to find articles related to specific points, such as "mHealth data in epidemiological studies." Articles were reviewed if their research focus was evaluating mHealth data or related aspects such as digital endpoints measured from mHealth data or if they included mHealth tools in their study design thus providing information relating to the utility of mHealth data in study designs. Studies were excluded if their research focus was solely on mHealth tools as a health intervention, for example looking at the efficiency of different forms of therapy delivered through a smartphone for patients struggling with mental health where the paper does not discuss mHealth data but rather the therapy intervention.

Given the large volume of results the most relevant and recent articles were prioritized. Using the "sort by relevance" filter on Embase the first 500 abstracts of the search results were scanned, though after roughly 350 articles, a point of saturation was reached meaning the remaining papers did not contain new use-cases for mHealth data, or new information on data collection or analysis methods relevant to the scope of this paper. To ensure that appropriate representation was achieved, every 10th page of the remaining search results was checked but no new relevant concepts were discovered. Using the "sort by date" filter, the abstracts of the first 500 of the most recent articles were scanned to ensure the inclusion of most recent developments otherwise not captured by the currently available systematic reviews and meta-analyses. In addition, a free internet search was conducted to look for initiatives relevant to mHealth data.

9.1.1. Search Terms

Subject Head Search Terms:
mHealth OR 'mobile health' OR ehealth OR 'digital health' OR wearable* OR ipad* OR 'mobile device' OR 'health digitali?ation' OR 'digital health technolog*' OR smartphone* OR 'e-patient*' OR 'remote patient monitoring' OR 'digital patient*' OR 'online patient*' OR 'wearable device' OR 'telemonitoring'

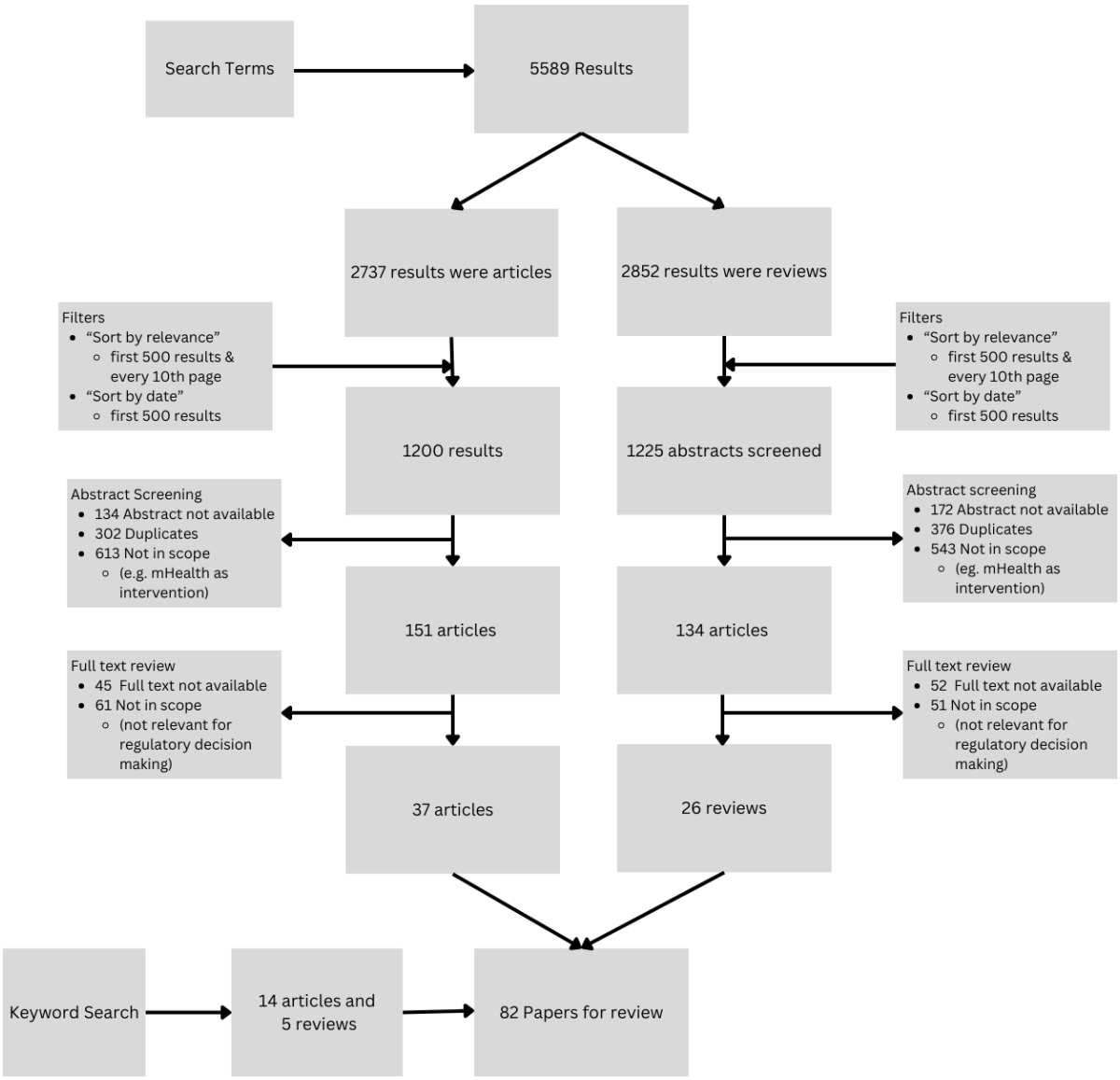
AND

'risk minimi?ation' OR 'medicine regulation' OR pharmacovigilance OR 'adverse drug reaction' OR regulator* OR 'regulatory decision making' OR 'clinical decision making' OR 'medical decision making' OR 'shared decision making' OR 'drug* regulation*' OR 'narcotic* control*' OR 'drug* control*' OR 'marketing authori?ation' OR 'drug* approval*' OR 'approval procedure*' OR 'approval process*' OR 'medicine* approval*' OR 'drug* assessment*' OR 'medicine* assessment*' OR 'drug* evaluation*' OR 'medicine* evaluation*' OR 'european medicines agency' OR 'food and drug administration' OR 'adverse drug event*' OR 'side effect*' OR 'adverse reaction*' OR 'adverse event*' OR 'drug monitoring' OR 'drug surveillance' OR 'post marketing authorization' OR 'drug safety' OR 'benefit-risk' OR 'risk assessment' OR 'drug efficacy' OR 'drug effectiveness'

Key Word Searches

'mHealth data for drug utilization studies'
'mHealth data in disease epidemiology'
'wearables and sensor accuracy'
'mHealth apps and ADR'
'Data Protection for mHealth data'
'Bias and Confounding in mHealth data'
'mHealth data Artificial Intelligence'

9.1.2. Search strategy visualisation



9.2. Tables

Table 2. The types of sensors and the measures they are used for in common currently available mHealth devices (Ates et al., 2022; Bayoumy et al., 2021; Bulling & Gellersen, 2010; Chakrabarti et al., 2022; Moon et al., 2023).

Sensor	Measurement	Purpose	device
Galvanic Skin Response (GSR)	Skin conductance	Stress level assessment, emotional state tracking, reaction to smells	Smartwatches
Ambient Light Sensor	Ambient light intensity	Sleep quality assessment, circadian rhythm monitoring	Smartphones, Fitness Trackers
Electrocardiogram (ECG)	Electrical activity of the heart	Measuring heartbeat through electrical changes in skin OR reaction to sensory input like smells	Watches, patches, armband, headband
SpO2 (Oxygen Saturation)	Oxygen Saturation (SpO2)	Respiratory and circulatory health assessment	Smartwatches, fitness trackers
Photoplethysmography (PPG)	Blood Volume Pulse (BVP)	Estimation of heart rate and its variation OR estimation of oxygen saturation in blood	Smartwatches, fitness trackers
Accelerometer	Acceleration	Activity tracking, step counting	Smartphones, Fitness Trackers
Thermometer	Skin temperature	Monitoring fever or changes in body temperature	Smartwatches, Smart Rings
Location Sensors (GPS, CDR (Call data record, Wi-Fi localization)	Geographical location	(in)activity, movement distance and patterns	Smartphones, Smartwatches
Gyroscope	Angular velocity	Orientation tracking, motion sensing	Smartwatches, smartphones
Magnetometer	Magnetic field strength	Compass functionality, orientation tracking	Smartphones, Fitness Trackers
Microphone	Audio	Breathing, cough, speech, eating	Smartphones
Electroencephalogram (EEG) & Electromyography (EMG)	Electrical activity of brain and muscles	Monitor, brain function, muscles and nerve cells	Smart headbands, Smartwatches
Electrogastrogram (EGG)	Electrical activity of stomach	Measuring stomach activity (gastric function)	Abdominal wearables,
Electrooculogram	Electrical activity of eyes	Measuring eye movement	Goggles, Headbands

Table 3. Challenges and opportunities for mHealth data use in regulatory decision-making

	Challenges	Opportunities
Operational	**Data Protection** ○ Insufficient data protection measures on many mHealth tools, potentially also increasing patient hesitancy to use such tools ○ Lack of transparency ○ Increased vulnerability to cyber attack	○ Protected data through EHRs and Registries ○ Data protection by default/design ○ Increased Patient engagement/trust
	Access ○ Restricted access by data protection regulation ○ Data storage (local, cloud etc.)	○ Passive generation of patient data ○ Readiness for Data linkage ○ Adopting new RWD
	Complex Regulatory Landscape ○ Different regulatory requirements by mHealth device type and purpose ○ Limited guidance	○ Consolidation of device, product, endpoint validation ○ Interdisciplinary collaboration ○ Leveraging mHealth data for most appropriate use-cases
Technical	**Data quality** ○ completeness and reliability ○ sensor accuracy, too loose of a fit, battery life, intentional falsification ○ Interoperability ○ unlabelled/unstructured data	○ Increasingly accurate and reliable mHealth data collection ○ Novel approaches (AI) to help overcome challenges
Methodological	**Study design** ○ Data collection Methods	○ Data collection efficiency and ease → remote/decentralized trials ○ Expansion of mHealth data use through validated parameters ○ Use for particular populations (paediatric, rare diseases etc.)
	Study Measurements ○ Bias/Confounding ○ Lack of agreed parameters and thresholds	○ Adaptable, accurate and reliable digital endpoints ○ Harmonized understanding of digital endpoints ○ Multimodal data collection
	Representativeness of data ○ Disproportionate use of mHealth devices	○ Patient experience data ○ Better reach and more diverse population ○ Remote, real-time data
	Data analysis ○ Large, unstructured data sets	○ Big data analytics ○ AI approaches

Table 4. Points for consideration for future actions for the utility of mHealth data.
The core points for consideration for future actions is to be realized through the reinforcing action and reflected in a strategic goal for the EMA.

	Core points for consideration for future actions	**Reinforcing Actions**	**Strategic goal**
Operational	Leverage work on patient experience data and expedite access to mHealth data	• Leverage work on PED to enable wider use and acceptance of mHealth data • Nurture access to mHealth data from companies or RWD pathways • Facilitate the creation of a common European patient data platform to allow for direct access to mHealth data from patients	To practice patient-centric drug development and enable wider use of mHealth data.
	Increase discoverability of data sources and studies using mHealth data	• Revise the meta-data fields to include 'mHealth data' or relevant terms for both submission and search of RWD sources and studies.	To increase transparency and discoverability of RWD studies and sources and enable efficient use of mHealth data
	Ensure compliance with data protection and ethical use of mHealth data	• Guidance on data protection measures for mHealth data for all stakeholders. • Evaluation of ethical use of mHealth data • Monitoring of AI act	Facilitate/promote early and long-term engagement with patients and ensure patient trust in the regulatory assessment
Technical	Engage and collaborate with all actors and relevant initiatives in the healthcare sector	• Public-private partnerships • Promote use of SA and ITF meetings • Precompetitive collaboration & sharing methods, outcomes & code between applicants • Leverage relevant initiatives to mHealth data use in medicine development or regulation • Consider needs of HTA and payers • Multi-stakeholder workshop on mHealth data	To ensure continuity and value of mHealth data across the product life-cycle and engage MA applicants and reimbursement stakeholders in the regulatory assessment.
	Engage with EU and international standards for mHealth	• Develop an mHealth data addition for Data quality framework • International standards like the IEEE standard for mHealth should be promoted • Inclusion of mHealth should be considered for the EMRN Data Standardisation strategy	To ensure use of high quality mHealth data, increase patient and stakeholder trust, enhance regulatory collaboration across the globe and advance regulatory science and mHealth research.
Methodological	Increase the understanding and tracking of the use of mHealth data in EU medicine regulation	• Detailed review of use of mHealth data in MAAs and SA documents • mHealth data use as a regulatory science research need	To stay at the forefront of mHealth data research
	Support the development of mHealth derived measures to	• Expansion of the qualified context of use for digital endpoints beyond specific device or disease	To facilitate faster development of reliable digital endpoints to ultimately speed up drug

	meet regulatory standards	• Ensure that work remains compliant and complimentary to MDR and pharmaceutical legislation • Assess feasibility of Joint SA for medical device & medicinal product	development and regulatory assessment.

9.3. Data Sources

9.3.1. mHealth apps

mHealth apps are widely accessible, with more than 400,000 health related apps available across app stores globally (van der Storm et al., 2023). The apps operate on smartphones or tablet computes and may work with multipurpose wearable devices like smartwatches or devices specific to that app. mHealth apps are designed for various purposes, most of them focusing on fitness, diet and/or lifestyle while more and more, especially since the COVID-19 pandemic, are made for disease monitoring, symptom reporting and health data sharing with HCPs (van der Storm et al., 2023). mHealth apps have various functionalities ranging from symptom reporting and activity logging to reminders about medication and treatment recommendations. From a regulatory point of view, mHealth apps have been shown to be especially effective for reporting of PROs and ADRs. In dermatology for example, skin cancer apps allow for patients to take pictures of formations on their skin and with the application of AI technology, the app can detect and classify the patients skin cancer based on the image. Not only could the data from these images be used to further understand the disease progression and variations of skin cancer, but they can also be used to support PAES studies. mHealth apps may come with functionalities to connect to and operate with different sensors on the smartphone or wearable devices. As such, they may have the additional ability to aggregate the data from smartphone sensors or wearables, such as heart rate and step count, to new measurements like daily physical activity. However, the reliability of these aggregate measurements is dependent on the accuracy of the sensors as well as the algorithm used to calculate it.

9.3.2. Wearables

Wearables are widespread with the number of globally connected wearable devices having surpassed 1 billion. Given their unique data collection features, wearables offer great potential to enhance regulatory decision-making. Wearable devices are equipped with various sensors meant to capture long term data on different biomarkers depending on their placement. Table 1. shows the types of sensors wearables today may come with and the health concepts they are able to measure.

Research grade wearables are more accurate and reliable as they have had to go through more rigorous testing compared to consumer grade wearables. However, several currently available consumer grade wearables have been used in health research considering great advancements in the accuracy and reliability of these devices for health data capture. For example, some currently available smartwatches use PPG heart sensors to measure heart function which have achieved more than 99% accuracy in measurements (Vijayan et al., 2021). Smartwatches have also been found to be effective in measuring other relevant aspects such as oxygen saturation and thus may be used for the detection of hypoxemia for example (Walzel et al., 2023). While the sensor itself might be accurate, other factors, such as the placement of the wearable and how well it is attached will impact the reliability of the results. Wearables are typically accompanied by an app which allows sharing of the patient data, as well as processing of the data and advanced analytics if the app is powered by AI or other tools.

9.3.3. Mobile devices

Mobile devices like smartphones and tablets are central in mHealth, being nearly ubiquitous in use globally while equipped with a plethora of sensors and connective capabilities to the Internet of Things. Their widespread use raises potential for cost-saving and far-reaching research opportunities, providing data which could be valuable for regulatory decision-making (Wall et al., 2023). Smart phones alone can be used to collect data on various biomarkers given the array of embedded sensors (see table 1.). Using accelerometers and gyroscopes, with the geospatial features like Bluetooth and GPS, smartphones can be used to measure movement type and frequency, useful for examining chronic diseases with movement-related symptoms like Parkinson's (Kulkarni et al., 2022). Smartphones may also be used to evaluate sleep or sociability by leveraging phone use factors like screen time, message logs or app usage, specifically on social media apps. However, compared to wearables, smartphones are not constantly attached to the body, and instead may either be carried in bags or left out of pocket (Wall et al., 2023). Smartphones are often used in mental health research as well, but their utility is characterized by the applications run on them. This limits the utility of smartphones for capturing clinical measurements on their own, yet their ability to connect to and share and analyse data with various other platforms or devices like wearables enhances their clinical relevance.

9.4. Initiatives

Table 5. Initiatives related to inclusion of mHealth data in regulatory decision making.

Initiative	Status	Topic	Country	Description
Initiatives funded under the Innovative Health Initiative (IHI)				
IDEA-FAST	Ongoing	Digital Endpoints and Measurements	International	Identifying digital endpoints to assess fatigue, sleep and activities in daily living in neurodegenerative disorders and immune-mediated inflammatory diseases
IDERHA	Ongoing	Data Processing and Management	International	Integration of heterogeneous data and evidence towards regulatory and HTA acceptance
MOBILISE-D	Ongoing	Digital Endpoints and Measurements	International	Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement
Trials@Home	Ongoing	Study Design	International	Centre of excellence – remote decentralised clinical trials
FACILITATE	Ongoing	Data Processing and Management	International	Framework for clinical trial participants data reutilization for a fully transparent and ethical ecosystem
H2O	Ongoing	Data collection and Standardization	International	H2O Health outcomes observatory
ConcePTION	Ongoing	Data Collection	International	Building an ecosystem for better monitoring and communicating of medication safety in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation
Gravitate Health	Ongoing	(Digital) Health Information	International	Empowering and equipping Europeans with health information for active personal health management and adherence to treatment
GetReal Initiative	Closed	Data Quality	International	The GetReal Initiative moves forward the implementation of the GETREAL project
RADAR-AD	Closed	Data Collection	International	Remote assessment of disease and relapse – Alzheimer's disease

Initiative	Status	Topic	Country	Description
COVID-RED	Closed	Data Collection	International	COVID-19 infections - remote early detection
RADAR-CNS	Closed	Data Collection	International	Remote Assessment of Disease and Relapse in Central Nervous System Disorder
EBODAC	Closed	Data Collection	International	Communication strategy and tools for optimizing the impact of Ebola vaccination deployment
WEB-RADR 2	Closed	Data Collection	International	WEB-RADR project created mobile applications (app) which allow patients and healthcare professionals to report adverse drug reactions (ADRs, or side effects) directly to the relevant authorities. The WEB-RADR 2 project aims to take the apps to the next level by making its functionalities available through application programming interfaces (APIs), and further mapping ADR terminologies.
RADAR-AD	Closed	Data Collection	International	Remote assessment of disease and relapse – Alzheimer's disease
Other Initiatives				
Parkinsons Progression Markers Initiative (PPMI)	Ongoing	Data Analytics	International	Parkinson's Progression Marker Initiative aims to identify biomarkers of Parkinson's disease.
Critical Path for Parkinsons Consortium 3DT Initiative (CPP 3DT)	Ongoing	Data Processing and Management	International	Collaborative Cancer Precision 3D Tissue Bioprinting Initiative for personalized medicine.
Clinical Trials Transformation Initiative (CTTI)	Ongoing	Medicine Regulation	International	Clinical Trials Transformation Initiative aims to modernize clinical trials and regulation.
Critical Path Institute's ePRO Consortium	Ongoing	Data Processing and Management	International	Develops electronic patient-reported outcome measures for clinical trials.
Real World Evidence Transparency Initiative	Ongoing	Data Protection	International	Aims to enhance transparency and trustworthiness of real-world evidence studies.
Structured Template for Planning and Reporting on RWE Study (STaRT-RWE)	Ongoing	Data Processing and Management	International	Provides a standardized approach for planning and reporting real-world evidence studies.
Digital Medicines Society (DiMe)	Ongoing	Data Protection	International	Promotes digital medicine by developing standards and best practices for data use and privacy. Created a library of digital endpoints.
EU Health Data Space	Ongoing	Data Processing and Management	European Union member states	Aims to create a single market for health data in the EU, facilitating research and innovation.
FDA's Digital Health Innovation Action Plan	Ongoing	Medicine Regulation	United States	FDA initiative to promote digital health innovation while ensuring patient safety.

Initiative	Status	Topic	Country	Description
Global Observatory for eHealth	Ongoing	Data Analytics	International	Aims to collect, analyse, and disseminate data on digital health technologies worldwide.
Label 2 Enable	Ongoing	Data Quality	Netherlands, EU	Aims to certify mHealth apps that are trusted and reliable through a certification scheme leveraging the ISO 82304-2

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