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Departamento de Ciências Médicas

Liliana Maria Rodrigues Teles

Potencial da mHealth e barreiras à sua adopção na União Europeia

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Bruno Gago, Professor Auxiliar Convidado do Departamento de Ciências Médicas da Universidade de Aveiro.

o júri

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palavras-chave

mobile Health, União Europeia, aplicações médicas, regulamentar, proteção de dados, interoperabilidade

resumo

Os sistemas de saúde Europeus defrontam-se com problemas de sustentabilidade financeira decorrentes de uma população envelhecida e do crescimento na prevalência de doenças crónicas. Mobile Health (mHealth), a prática médica apoiada por dispositivos móveis, tem o potencial para impulsionar o sector da saúde no sentido de uma prestação de serviços mais eficiente e centrada no paciente, estimulando a sustentabilidade económica dos sistemas de saúde. Apesar das promissoras projeções iniciais, a implementação da mHealth na União Europeia aparenta ter sido limitada por obstáculos estruturais e regulamentares.

Este trabalho visa desenvolver uma melhor compreensão sobre os mais relevantes desafios que previnem a ampla adoção da mHealth na União Europeia, focando particularmente nas aplicações médicas móveis.

A pesquisa por literatura científica sobre mHealth foi realizada na base de dados PubMed recorrendo a palavras-chave relevantes. Literatura cinzenta sobre mHealth foi propositadamente consultada e analisada para completar o estudo.

Além de capacitar o doente na gestão da sua própria saúde, a mHealth foca-se na prevenção da doença, na agilização do diagnóstico e na melhoria da adesão ao tratamento, portanto contribuindo para uma prestação de serviços de saúde mais eficiente e sustentável. A incerteza associada ao quadro regulamentar aplicável, a proteção de dados pessoais e a falta de modelos adequados de reembolso são apontados como principais barreiras a uma ampla adoção deste tipo de tecnologias. Um diálogo permanente e construtivo entre as partes interessadas é vital para garantir que soluções de mHealth, seguras e eficazes, são plenamente exploradas.

keywords

mobile Health, European Union, medical applications, regulatory, data protection, interoperability

abstract

European healthcare systems are struggling with financial sustainability problems arising from an ageing population and chronic diseases prevalence growth. Mobile Health (mHealth), the medical practice supported by mobile devices has the potential to drive the health sector towards a more efficient and patient-centered healthcare as well as stimulate health system economic sustainability. Despite the promising early projections, mHealth's deployment in the European Union seems to have been limited by structural and regulatory. This work seeks to develop a better understanding over the relevant challenges preventing the wide adoption of mHealth in the European Union, particularly mobile medical applications.

A search for empirical literature on mHealth was conducted on PubMed database using relevant key-words. Grey literature regarding mHealth was examined and purposively consulted to further inform the study.

Besides empowering patients in managing their own health, mHealth focuses on disease prevention, expediting diagnosis and enhancing treatment compliance, contributing to a more efficient and sustainable healthcare delivery. Regulatory uncertainty, data protection issues and lack of appropriate reimbursement models are appointed as main barriers to a wide adoption of this kind of technologies. An ongoing and constructive dialogue between relevant stakeholders is vital to ensure that safe and effective mHealth solutions are fully exploited.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADE	Adverse Drug Event
AIMDD	Active Implantable Medical Device
API	Application Programming Interface
Apps	Applications
CE	*Conformité Européene* (European Conformity)
COPD	Chronic Obstructive Pulmonary Disease
DPO	Data Protection Officer
ECG	Electrocardiogram
EC	European Commission
EEC	European Economic Community
EFTA	European Free Trade Association
eHealth	Electronic Health
EN/ISO	European Norm/International Organization for Standardization
EU	European Union
GDP	Gross Domestic Product
GPRS	General Packet Radio Service
GPS	Global Positioning System
HER	Electronic Health Record
IVD	In-Vitro Diagnostic Medical Device
IVDD	In-Vitro Diagnostic Medical Device Directive
MDD	Medical Devices Directive
mHealth	Mobile Health
NB	Notified Body
NHS	National Health Service
OECD	Organization for Economic Co-operation and Development
PDA	Personal Digital Assistant
PwC	PricewaterhouseCoopers
RCT	Randomized Clinical Trial
SMEs	Small and Medium-sized Enterprises
SMS	Short Messaging Service
UK	United Kingdom

1. INTRODUCTION

1.1. MOBILE HEALTH

Mobile Health (mHealth) is the "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices". It includes mobile applications (apps) for medical or for general fitness/wellbeing purposes that may connect to medical devices or sensors (e.g. bracelets or watches) as well as personal guidance systems, medication reminders provided by short messaging service (SMS) and telemedicine provided wirelessly. [1]
mHealth is embedded in the so-called Electronic Health (eHealth), a branch of healthcare that makes use of computers, emails, satellite communications and monitors to deliver healthcare services. mHealth technology performs similar functions, but on portable devices. mHealth allows the provision of care to patients or technical support to healthcare professionals in a direct, low-cost and engaging manner. [2]
It can be used for a wide range of purposes, including health promotion, illness prevention, disease surveillance, treatment support, disease management, clinical decision making support, clinical record keeping, real-time health information stream, education and awareness. Prominent examples of mHealth are software apps intended to be used as communication, information and motivation tools, as well as for disease prevention, diagnosis and treatment. [3, 4]

In accordance with the Global Observatory for eHealth, mHealth involves the use of a mobile device's core utility of voice and SMS as well as general packet radio service (GPRS), third and fourth generation mobile telecommunications (3G and 4G systems), Wifi (technology that allows electronic devices to connect to a wireless network), WiMAX (family of wireless communication standards), computer-based technologies, global positioning system (GPS), and Bluetooth technology for short-range communications.
These technologies operate on hardware platforms that include mobile smartphones, mobile computers (netbooks, tablets, and PDAs), pagers, digital cameras, and remote sensors. [4] Technically, mHealth implies a wireless broadband electronic communications infrastructure, an electronic platform, downloadable software and specialized applications and connected mobile terminal equipment, either common (telephones, tablets, PDA) or specific (implantable or non-implantable). [5]

The expanding spread of smartphones equipped with 3G and 4G networks, the availability of satellite navigation technologies as well as the growing device's capability of storing and processing data, boosted the growing number of applications offering healthcare related services that have been developed for smartphones, most of them accessible to the general public through online application stores. Smartphones are affordable, multi-use and portable computing platforms whose apps can be downloaded, installed,

updated and accessed with a simple tap of a finger. [3, 4] The software platforms are diverse, from open-source operating systems like Google's Android and Nokia's Symbian to proprietary ones like Apple's iOS and Microsoft's Windows 7 Mobile. [6]

1.2. Opportunities of Mobile Health

Healthcare systems worldwide are struggling with financial sustainability problems arising from an ageing population and chronic diseases prevalence growth. Europe's population aged 65 and over is projected to rise from 129 million in 2010 to 224 million by 2050; with the number of people 85 years and older expected to rise from 14 million to 40 million. [7]

Data from 2012 show that 52% of the European Union (EU) population is overweight, 17% of which are obese. Also, although smoking habits have declined in most EU countries, on average one-fifth of adults still smoke. [8]

According to the Organization for Economic Co-operation and Development (OECD), the prevalence of patients suffering from chronic diseases such as type 2 diabetes, chronic obstructive pulmonary disorders and cardiovascular diseases are creating a significant burden on EU's already constrained healthcare systems' budgets. About 10% of the total annual healthcare expenses in the EU are spent on the treatment and monitoring of Type 1 and Type 2 diabetes which, when poorly managed, result in significantly higher number of hospital admissions and increasing consumption of human and economic resources. [2] Data from a 2015 report by the OECD show that, on average, EU Member States spent 8.7% of their GDP and about 15% of total government expenditure in healthcare. [8] Furthermore, healthcare expenses in most Member States have been rising faster than government investment (due to the 2009 economic crisis, several European countries cut significantly their healthcare spending) and citizens' out-of-pocket contributions. [9].

Nowadays healthcare services are shifting from acute/hospital care to continued, community-based and patient-centered care. Patients are becoming more and more empowered and demanding for services that more willingly acknowledge their preferences with a high degree of quality. [10, 11] Huge technological developments and increasing patient's empowerment and demand became strong drivers for innovative and adaptive solutions for healthcare delivery. The rapid penetration of smartphones and tablets, the thriving opportunity of device portability and the ubiquitous and accessible connectivity of mobile technology and networks further contributed to it. [1] mHealth became an exceptional opportunity to improve information access and to provide personalized medical care that fits the patients' specific needs. Evidence showed that mHealth is capable of delivering preventive, patient centered healthcare while improving some services efficiency. [12] This naturally led to mHealth's emergence as a complementary tool for delivering efficient and sustainable healthcare.

1.3. Economic Potential of Mobile Health

A joint analysis by GSMA and PwC estimates that the global mHealth market will reach the equivalent of US$ 23 billion by 2017, with Europe accounting for US$ 6.9 billion, Asia-Pacific for US$ 6.8 billion and the North American market for US$ 6.5 billion. Predictions of financial analysts estimate that the global market for mHealth technology will grow at an annual rate of nearly 55%, from US$ 1.5 billion in 2012 to US$ 21.5 billion by 2018. [13-15] The global mHealth monitoring and diagnostic market was valued at US$650 million in 2012, and is projected to reach US$8 billion in 2019. [16] Wireless subscriptions' growth, which has already reached over 6 billion worldwide, has greatly favored the uptake of the mobile «health and wellbeing» market. [3, 17]

Another study conducted by GSMA and PwC indicates that in 2017 mHealth could potentially save €99 billion in healthcare costs in the EU. The largest savings are expected to be in wellness/prevention (€69 billion) and treatment/monitoring (€32 billion) considering the costs of the workforce needed to support mHealth activities (€6.2 billion). [3, 18] The same study projects that the implementation of mHealth solutions in EU healthcare settings can potentially benefit 185 million patients by improving the way they manage their medical conditions and enable 11.2 million chronic patients and 6.9 million patients at risk of developing chronic diseases to extend their professional lives and improve their productivity, contributing with up to €93 billion more to EU's GDP in 2017. [2]

mHealth is likely to be a large value creation opportunity for multiple stakeholders. According to the PwC and GSMA report, *Touching lives through mobile health: Assessment of the global market opportunity*, mobile operators are expected to be the key beneficiaries of mHealth's market growth and, by 2017, to command about 50% of overall market shares, amounting to US$ 11.5 billion. Other beneficiaries will be device vendors (29%), content/application developers (11%) and healthcare providers (10%). Mobile operators are increasingly acting as system integrators to bring total remote patient monitoring systems to the market, thus boosting its revenues. In the diagnostic market, existing healthcare providers will garner most of the revenues. [19]

1.4. Mobile Health Apps

"App", short for "application (program)", refers to a self-contained piece of software coded for a specific purpose and usually optimized to run on a mobile device. [12]

A 2016 GSMA report shows that, by the end of 2015, there were 4.7 billion mobile subscribers globally, equivalent to 63% of the world's population. By 2020, almost three-quarters of the global population will have a mobile subscription, with around 1 billion new subscribers added over the period. [20]

The growth in the mobile devices market, mostly smartphones and tablets, boosted by the growing number of wireless subscriptions, has been accompanied by a rapid increase in the number of software applications designed for mobile devices. With more than 1600 new apps added to app stores daily, the mobile apps market became a key driver for mHealth. [3, 19, 21-23]

Mobile medical apps generally serve multiple purposes, including treatment support, disease management and surveillance; data collection; health promotion and disease prevention; communication between patients and health care providers or among healthcare professionals; and health education/training. [24] Its usefulness can stretch from simple text message reminders to apply sunscreen or promote adherence to treatment, to sophisticated apps that coordinate the management of diabetes. [12]

Currently over 100,000 mHealth apps are available on major app stores on the global market. 70% of mHealth apps target the consumer wellness and fitness segments; the other 30% target health professionals, facilitating diagnosis, monitoring, access to health data and patient consultation. [3]

According to the latest projections by mobile research specialist group Research2Guidance, by 2017, 3.4 billion people worldwide will own a smartphone and half of them will be using mHealth apps. [13, 17] The "*Global Mobile Health Market Report 2013-2017*" states that 9% of the total mHealth market revenue will come from application downloads, while 84% of total mHealth application market revenue will come from related services and products such as sensors. [13]

2. METHODS

This dissertation has drawn on relevant scientific literature in order to contextualize the potential benefits of mHealth as well as main barriers to its full deployment within the European Union.

A search for empirical literature on mHealth and mobile medical apps was conducted on PubMed database using the following key-words: “Europe”, “health”, “medical”, “mobile”, “software”, “device”, “mHealth”, “adoption”, “potential”, and “challenge”. Related words, truncation, Boolean operators and proximity search techniques were used to refine the literature search, as follows: (((((“Europe") AND (health* OR medic* OR clinic* OR care)) AND (("mobile" adj1 (software OR app* OR device)) OR "mHealth" OR "m-Health")) AND (adoption OR accept* OR embrace* OR endorse*) AND (challenge OR barrier OR obstacle OR potential OR benefit OR advantage)). The literature search was conducted in English and the results were limited to English. A total of 255 results were found; each abstract was reviewed. 43 papers were considered to be relevant for the study and therefore were used. The remaining results were excluded.

Grey literature regarding mHealth was examined and purposively consulted to further complete the study, including European Commission policy reports and position statements; international health agencies’ policy, technical and financial reports; and private organizations strategic documents and market assessments. Additionally, EU regulatory frameworks on medical devices and data protection were consulted. All documents were obtained from institutional web-based platforms publicly accessible. The main institutional sources were found using Google search engine for significant key-words, namely “mHealth”, “mobile health” and “mobile medical apps”.

3. MOBILE HEALTH POTENTIAL IMPACT ON HEALTHCARE

Health mobile applications and technologies will transform the way the entire healthcare system operates, representing an immense opportunity to enable physicians and patients to manage care in new, fast, efficient and personalized ways. [2, 25] A description of the potential benefits of mHealth, illustrated by examples of mHealth apps already on the EU market, is presented below.

3.1. More Efficient and Sustainable Healthcare Delivery

mHealth reduces unnecessary face-to-face consultations and visits to hospitals, with medical interventions being done remotely through mobile-based communication technologies, guided by monitoring and data reporting systems. [2] As an example of the benefits of remote monitoring, a smartphone connected via Bluetooth to a single-lead electrocardiograph device can have a role in walking-based cardiac rehabilitation in patients unable to attend traditional hospital-based rehabilitation. A small study followed 6 patients who had a recent coronary event, throughout their after-surgery home based exercise routines. A mHealth app tracked the patients' heart rate, single-lead rhythms and GPS-based speed and location while transmitting this information to a secure cloud server for real-time monitoring by a qualified healthcare professional. The researchers concluded that this was a feasible and flexible way of providing supervised cardiac rehabilitation for patients unable to access hospital-based programs while at the same time improving quality of life, as stated by the patients on questionnaires. [26]

mHealth has the potential to increase treatment compliance and avoid disease complications and associated costs using remote interactions to monitor patients in their homes. [2] In fact, trials in Nordic countries show that mHealth could generate a 50-60% reduction in hospital nights and re-hospitalization for patients with chronic obstructive pulmonary disease (COPD). [27] Results from pilots and projects in Scotland and Norway estimate that mHealth could reduce overall elderly care expenditure by 25%. [2] Additionally, it can aid in hospitalization reduction and enable healthcare resources to treat and monitor more patients at the same time. [2] By the means of mHealth, healthcare providers can support chronic patients in improving their lifestyles and monitor their diet, physical activity and medications, allowing to customize and improve care. By doing so, PwC estimates that 11.2 million chronic patients in the EU could better manage their conditions by 2017. By reducing the severity and incidence of chronic diseases, mHealth solutions could save a total of €32 billion in treatment costs, allowing healthcare delivery systems to better cope with reducing budgets. The increased availability of healthcare resources would allow healthcare systems to treat additional patients. [2]

Through education and awareness, mHealth can positively influence citizens' behavior and lifestyle thus improving clinical outcomes. mHealth allows for the collection of considerable medical, physiological, lifestyle, daily activity and environmental data. Analysis of this big data may help improve healthcare effectiveness and disease prevention by providing the basis for evidence-driven care practice and research activities, while facilitating patients' access to their health information anywhere and at any time. [3] A good example is *Medipal*, a smartphone app intended to improve doctor-patient communication. The healthcare provider creates a *Medipal* account for the patient, and interacts remotely with him through questions and answers. This interaction not only increases the patient's involvement in its own care but also helps doctors to stay engaged with their patient's treatment plan even if the patient doesn't visit the hospital. [2]

Estimates show that the use of tablet computers and other mobile devices could help healthcare professionals and paramedic staff save up to 30% of their time spent on accessing and analyzing health data. [3] Thus, mHealth can provide better treatment planning and give health professionals more guidance throughout decision-making processes. [2]

3.2. Focus on Prevention

mHealth motivation and user engagement tools can play a big role in disease prevention. mHealth is able to provide patients with relevant health information on their mobile devices that can be used to make improved and more informed choices concerning their lifestyle behaviors. Interactive mHealth solutions can motivate patients to healthy attain everyday goals and stay motivated in the long-term. A more engaged population with healthier lifestyles is expected to create less financial pressure on healthcare systems. [3, 28] In this context, there are some well-known examples of disease prevention and health promotion apps already on the market: *Exsmokers iCoach,* a mobile application developed with European Commission's funds that helps individuals quit smoking. It provides tailored feedback, advice, techniques, tasks, as well as mini tests, and sends the user daily emails as reminders for motivation; *Diabetes App – blood sugar control, glucose tracker and carb counter,* a mobile application for diabetes self-monitoring and data management, that allows the user to log and track factors which influence blood-sugar level; additionally, it allows networking with other people like family or friends and provides support dealing with symptoms/disabilities; and *SAPO Fit,* a mobile application to control obesity that enables users to track in real time their food intake and daily exercise and to share this data in social networks, encouraging optimization of one's wellness regime. [29]

Taking into account that 8% of smokers quit smoking successfully if constantly motivated and reminded; that 60% of at-risk diabetics can avoid type 2 diabetes through healthy diet and adequate exercise; and 34% of obese people benefit from personalized weight loss program and counselling, mHealth tools can play a big role in chronic disease prevention. [2, 8]

3.3. Expediting Diagnosis

Delay in diagnosis of chronic diseases increases complications and treatment costs. 50% of patients are usually not aware of the causes and symptoms of their disease with most chronic diseases getting diagnosed only when complications appear. This leads to a higher severity of the disease at the moment of diagnosis, resulting in increased hospitalization rates and higher treatment costs. [2, 28]

By using self-assessment and remote diagnosis/monitoring tools, mHealth can help detect the development of chronic conditions at an early stage, facilitating timely medical interventions. [2, 3]

Some studies undertaken by the United Kingdom's Department of Health have shown that the use of technology for remote monitoring and intervention, if correctly used, can deliver a 20% reduction in emergency admissions and 14% reduction in bed days. [30] Targeted at expediting diagnosis, *AirStrip CARDIOLOGY,* a smartphone application intended for remote diagnosis and treatment decision-making for heart patients, enables clinicians to check electrocardiograms with enhanced analytics on their mobile devices, anywhere and anytime. It helps clinicians making faster, more informed diagnosis and treatment decisions, expediting medical interventions and preventing heart damage. [29] In the same perspective, *ONCOassist – Decision Support System,* an app for iPhone and iPad designed by oncology professionals, contains prognostic tools and useful calculators for oncologists at the point-of-care, saving clinicians valuable time. [12, 31]

mHealth solutions can educate patients on symptoms of disease, helping them understand if and when they need to undergo diagnostic tests. Some also allow patients to store the results of diagnostic tests on their mobile devices and share these with the healthcare provider, eliminating the need of hospital visits. As an example, *Lab Tests Online*, a free smartphone app, allows storage of diagnostic tests and helps users understand the results of those tests providing information on the contribution they make to the treatment process. [29]

PwC estimates that increasing effectiveness and efficiency of care through educational and algorithmic solutions that allow patients to self-assess symptoms can help 9.4 million regular users at risk of developing chronic diseases to expedite diagnosis. [2] Accounting for the prevalence of various chronic diseases in the EU, PwC estimates that 815 000 patients could successfully detect chronic diseases at an early stage if given the proper knowledge and tools to do it. These patients could avoid complications and seek medical attention earlier, reducing the need for hospitalization and saving €3.7 billion in treatment costs. [2]

3.4. Enhancing Treatment Compliance

Treatment nonadherence is a common, complex, and costly problem that contributes to poor treatment outcomes. Emphasis is given to medication nonadherence where patients take medication incompletely, inconsistently or not at all. [32] Medication adherence apps can be downloaded for little to no cost, provide patient-specific information and are most useful for patients with complex medication regimens. [33] Improved adherence and continuous remote treatment of chronic conditions using mHealth can help avoid severe complications and improve clinical outcomes. [1, 3]

The number of apps aimed at organizing and taking medications is increasing across the dominant smartphone platforms. Among the currently marketed treatment adherence apps, features include reminders for consumption and refills, data logs accessible by patients or care providers, and medication information (e.g., dosages, adverse effects) all of which readily accessible with the touch of a finger. [32, 33] The European Commission's directory of heath apps includes examples of apps targeted at improving treatment adherence and compliance. *Med Helper – Pill Reminder and Medication Tracker* is a smartphone app that provides reminders when to take medication. Features alarm reminder, log of past doses, multiple profiles for more than one user, facility to record pharmacy and healthcare professional contact details as well as exportable reports; [29] *Care4Today Mobile Adherence Medication Reminder Platform* is a free app developed by Janssen Healthcare aimed at improving adherence to treatment regimens through self-directed reminders to take medications, refill prescriptions and visit healthcare providers. [34]

3.5. Improved Data Capture and Data Access

Mobile devices such as smartphones and tablets can improve patient data collection at the point of care. This prevents more data entry errors than if information were first recorded on paper and later entered into the patient's electronic health record by administrative personnel. Mobile smartphones and tablets also allow healthcare professionals to access critical patient information from any place at any time. [3, 35]

3.6. Improved Treatment Accuracy

mHealth can support the delivery of high-quality healthcare, being instrumental in increasing the accuracy of diagnosis and treatment and the decision-making process. [2, 3] It is estimated that practitioners spend 25% to 30% of their time gathering and analyzing patient's medical data to make decisions about their treatment. Mobile tablets and smartphones can be clinical decision supporting tools that ensure healthcare professionals are providing patients the best treatment plans within the smallest timeframes. [36]

The lack of readily available and up-to-date medical information can result in uninformed clinical decisions. Such decisions can lead to prescription and dosage errors, creating adverse drug events (ADEs) that cost EU healthcare systems €2.7 billion per year in care costs and account for 1.1% of hospitalizations. [2] *Epocrates,* a mobile app available for all smartphone platforms that offers up-to-date pharmacologic information, is intended to support the delivery of high-quality healthcare. Strengths of this app include drug dosage guidelines, adverse reactions, mechanisms of action, and a drug interaction checker. One out of two US physicians rely on *Epocrates* to enable better patient care. [29] Additionally, tablets equipped with electronic health record software and barcode readers are being leveraged to scan patient wristbands in hospital settings and ensure that the right drug, in the right dose, is being administered to the right patient, at the right time. This helps eliminate the potentially life-threatening adverse drug events that often occur due to medication errors. [37] Currently there is a broad range of apps that assist clinical practice at the point of care: drug reference guides, medical calculators, clinical guidelines and other decision support aids, textbooks, and literature search portals. [29]

3.7. Patient Empowerment

Even though mHealth is not intended to replace healthcare professionals, it can greatly contribute to patients' empowerment in the management of his own health. [2] Through mobile applications intended for self-assessment, remote treatment monitoring or improvement of treatment compliance, mHealth allows patients to access their personal health data on demand, manage their health records and monitor chronic conditions such as diabetes and hypertension in real-time, outside of the hospital setting. These possibilities change the patient's role from a passive to a more participative one, bringing more balance to the doctor-patient asymmetrical relationship. It can also raise the patients' awareness about health issues using easy-to-understand information, thus helping them make informed decisions about their lifestyles and health behaviors. [3]

OnTrackDiabetes is an app intended to help diabetic patients to take control over their disease and delay diabetes complications by self-monitoring blood glucose, blood pressure, pulse, weight, medication, exercise and diet. It generates interactive reports that can be shared with their doctor for further analysis. Also directed at empowering patients, *Blood Pressure Log* is a smartphone application intended to involve hypertensive patients in managing their own condition. It helps patients self-monitor blood pressure values and determine whether these are normal, high, or at hypertension; *AliveCor Heart Monitor*, a mobile electrocardiogram device in combination with the smartphone app *AliveECG* provides individuals with the ability to track heart health anywhere and anytime. It enables the recording, displaying, storing and transfer of single-channel electrocardiogram readings to health professionals via e-mail. *AliveCor Heart Monitor* has been assessed in several clinical trials and demonstrated enough accuracy and efficiency for both single-channel rate and rhythm assessments. [29]

4. SLOW ADOPTION OF MOBILE HEALTH IN THE EUROPEAN UNION

The potential benefits of mHealth could positively contribute to tackle healthcare challenges faced by professionals, patients and authorities/governments while promoting personalized health monitoring and treatment, reducing the costs of disease management and integrating, transferring and storing health data easier. Given all these possibilities and the prodigious advance in mobile technology, it is somehow surprising that the adoption curve of mHealth interventions keeps flatten. [2, 21] Although initial estimates of mHealth benefits provided by ongoing mHealth pilots and expert opinion have been promising, there is a strong possibility that these potential benefits are limited by several structural and regulatory roadblocks to adoption. [2, 38, 39]

4.1. Regulation of Mobile Apps as Medical Devices

The advent of new forms of healthcare assisted by communication technologies such as mHealth and particularly mobile medical apps, has created new challenges largely regarding regulation. The mobile medical apps market continues to innovate at an outstanding pace. Additionally, the medical and telecommunications devices are growingly converging, making it more complex to elaborate applicable regulations. [39]

The potential benefits for patients and healthcare providers are promising, but app developers and authorities must prevent potential consequences resulting from an incorrect use within medical context. Ensuring the safety and performance of mobile medical apps is imperative and requires regulators to balance consumer safety with software innovation. Patient's safety should be at the center of mHealth solutions and is essential in creating the foundations to ensure trust in and scalability of mHealth services.

In the EU, mobile medical apps with an intended medical purpose are mHealth devices which fall under the definition of medical device and are regulated under the "New Approach" Directives. [40]

EU's governing body responsible for medical device regulation is the European Commission (EC). It is tasked with protecting the consumers from devices that are unfit for purpose and potentially damaging to health. [39]

The main EU directives relating to the safety and performance of medical devices are:

- Directive 93/42/EEC on medical devices (MDD);
- Directive 90/385/EEC on active implantable medical devices (AIMDD);
- Directive 98/79/EEC on in vitro diagnostic medical devices (IVDD).

These Directives have been supplemented and amended by Directive 2007/47/EC.

The Directive that specifically covers the European classification of medical devices and their accessories is the Medical Device Directive 93/42/EEC. The MDD defines what constitutes a medical device, how medical devices should be regulated according to different classifications, and how devices should be marked to demonstrate their conformity with essential requirements. [41, 42]
According to the MDD, medical device means "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception;

which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. " [43]

Applicability of the MDD to a product is based on its intended purpose grounded on the claims made by the manufacturer on the label, instructions for use and promotional materials. [43] A product's intended use in combination with the definition of what constitutes a medical device enables manufacturers to decide with reasonable clarity whether the product will fall within the scope of the Directive.

Once it has been established that a product meets the definition of a medical device, the manufacturer can undergo the conformity assessment procedures in order to demonstrate that it meets the relevant requirements for safety and performance that are set forth in the relevant Directive. The procedure for conformity assessment under the MDD (Annex IX) is risk-based and allows for a graduated system of control - the higher the class, the more stringent conformity assessment procedures. [43]

The MDD divides medical devices into either Class I, Class I (sterile), Class I (measuring function), Class IIa, Class IIb or Class III, according to the risk of harm to the patient, with Class III being for medical devices with the highest risk. The process of deciding the risk class assigned to a medical device is facilitated by rules defined according to the device's invasiveness (invasive, non-invasive), duration of contact with the body (transient, short term, long term), dependence on an electrical source (i.e. active medical devices), among other criteria. [43]

The regulation of medical devices in the EU is governed by the CE marking. When a medical device bears the CE Marking it means that it has been shown, through conformity assessment procedures, to meet essential requirements for safety and performance stated in the MDD. Bearing the CE Marking means that the device

was designed and manufactured in such a way that, when used under the conditions and purposes intended, it does not compromise clinical conditions or safety. Additionally, a CE-marked medical device can be freely traded throughout all of the European Union member states and the wider European Free Trade Area (EFTA). Medical devices not CE-marked are not allowed in the EU market. [44]

To achieve the CE marking, the manufacturer must compile technical documentation for each device providing evidence that the device fulfils the essential requirements for performance and safety that are set out in the applicable Directive. The conformity assessment procedure also involves the demonstration that there is a suitable quality management system in place to control design, manufacture and post-market surveillance of the device. [43]

Up from class I (non-sterile, non-measuring), the conformity assessment procedure must involve a third party controlling organization referred to as a Notified Body (NB). The NB ensures that, before placing a medical device on the EU market, it conforms to the applicable requirements, through technical file assessments, quality management system's audits and certification. If a manufacturer complies with the safety and performance requirements applicable to the device, the NB issues a CE certificate and authorizes the manufacturer to label the device with the CE-marking. [45] This certification have an expiry date, typically 5 years. After the certificate expires, the CE Marking of the device is no longer valid and the manufacturer must apply again to the conformity assessment procedure in order to maintain his devices compliant. The conformity assessment procedure for Class I devices is performed by the manufacturers themselves, the so called «self-declaration of conformity». For this class there is no intervention of a NB and the manufacturer bears all the responsibility to ensure that the essential requirements of the applicable Directive are met and the device is considered safe for its intended use. [43]

Under the MDD, prior to placing a medical device on the market, manufacturers are required to register with their Competent Authority. Additionally, once CE Marking has been obtained and the device has been placed on the EU market, the manufacturer is obliged to have post-market surveillance procedures in place to monitor the performance of the device and to identify and report incidents to the national competent authorities.

Focusing specifically on mobile apps that fall under the definition of medical device, the MDD is the primary source of regulation across European Member States. [43]
As described, determination with respect to applicability of the MDD to a product is based on the intended purpose of the product, the claims alleged about its function and its mode of action. Both embedded and stand-alone software (e.g., mobile medical apps) can qualify as a medical device if the developer's intention was that the software should be used, alone or in conjunction with other device, for a specific medical purpose. [43]

Aiming to cope with the growing development of software with a medical purpose, the MDD was revised through Directive 2007/47/EC, making clear that standalone software with a medical purpose are medical devices and therefore are subject to the Medical Device Directives. Recital 6 of Directive 2007/47/EC states that "it is necessary to clarify that software in its own right, when specifically intended by the manufacturer to be used for one or more of the medical purposes set out in the definition of a medical device, is a medical device. Stand-alone software for general purposes when used in a healthcare setting is not a medical device." Under the current rules, devices that incorporate software, or that are medical software in themselves, must be validated according to the state of the art, taking into account the principles of development lifecycle, risk management, validation and verification as with "traditional" medical devices.. [46]

The amended MDD was still considered unclear about how to properly classify health apps or software. Since the software is not physically tangible, the application of the requirements in the Directives is not always entirely clear. In order to help software developers and manufacturers identify if their products fall under the applicable Directives, "*Guidelines on the Qualification and Classification of Stand Alone Software Used in Healthcare within the Regulatory Framework of Medical Devices*" (MEDDEV 2.1/6, last updated on January 2012) has been issued separately by the EC, providing more precise definitions, eligibility criteria, decision trees and examples. According to this guidance, depending on their intended purpose, mobile apps may fall under the definitions of a medical device or an in vitro diagnostic medical device and consequently will have to comply with the relevant provisions of the aforementioned Directives. [47] Software falling outside of the definition of medical device will nevertheless be regulated as a "medical device" if it is intended by its developer to be used as an "accessory" to one or more medical devices, i.e., to enable a product classified as medical device to be used for its intended purpose. Many apps may, therefore, be classified as accessories; the medical devices they serve, wherever located, will fall under the same EU legislative framework. [43, 48]

Pursuant to this guidance, a stand-alone or embedded software must fulfil the following criteria in order to be qualified as a medical device:

- The software has a different purpose than mere storage, archival, lossless compression, communication or simple search of health-related data, that means, software is intended to create or modify medical information to facilitate diagnostic or therapeutic decisions;
- The software has to be for the benefit of individual patients;
- The software has to have an intended purpose listed in Article 1(2)a) of Directive 93/42/EEC.

Indicative intended purposes for qualification as a medical device are among the following:

- Decision support or decision making software e.g. with regard to therapeutic measures;
- Calculation of dosing of medicines;
- Monitoring patients and collecting data if the results thereof have an influence on diagnosis or therapy.

MEDDEV 2.1/6 clarifies that stand alone software with a medical purpose is considered to be an active medical device, given that its operation “depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy.” As so, for the classification of stand-alone software and determination of the conformity assessment procedure required for CE marking, rules 9, 10, 11 and 12 of Annex IX to Directive 93/42/EEC, as well as clause 2.3 of the implementing rules in Annex IX, may apply:

Rule 9

"All active therapeutic devices intended to administer or exchange energy are in Class IIa unless their characteristics are such that they may administer or exchange energy to or from the human body in a potentially hazardous way, taking account of the nature, the density and site of application of the energy, in which case they are in Class IIb. All active devices intended to control or monitor the performance of active therapeutic devices in Class IIb, or intended directly to influence the performance of such devices are in Class IIb."

Rule 10

"Active devices intended for diagnosis are in Class IIa, if they are intended to supply energy which will be absorbed by the human body, except for devices used to illuminate the patient's body, in the visible spectrum; if they are intended to image in vivo distribution of radiopharmaceuticals; if they are intended to allow direct diagnosis or monitoring of vital physiological processes, unless they are specifically intended for monitoring of vital physiological parameters, where the nature of variations is such that it could result in immediate danger to the patient, for instance variations in cardiac performance, respiration, activity of the central nervous system, in which case they are in Class IIb. Active devices intended to emit ionizing radiation and intended for diagnostic and therapeutic interventional radiology including devices which control or monitor such devices, or which directly influence their performance, are in Class IIb.“

Rule 11

“All active devices intended to administer and/or remove medicines, body liquids or other substances to or from the body are in Class IIa, unless this is done in a manner that is potentially hazardous, taking account of the nature of the substances involved, of the part of the body concerned and of the mode of application in which case they are in Class IIb.”

Rule 12

"All other active devices are in Class I."

Implementing rule 2.3

"Software, which drives a device or influences the use of a device, falls automatically in the same class."

According to these rules, most medical apps determined as medical devices are usually classified as Class I (unless they have a measuring function), which represents the lowest risk of potential patient's harm and involves only a small number of regulatory requirements (not requiring the intervention of a NB, for example). However, these rules also show that a mobile app can potentially be classified as Class IIa or IIb, requiring the involvement of a NB in the CE marking process. As examples, an insulin dosage planning stand-alone software would fall under classes IIa or IIb; software for the presentation of the heart rate for intensive care monitoring is an active device intended for the monitoring of vital physiological parameters where the nature of variations is such that it could result in immediate danger to the patient, falling under class IIb; active devices intended for diagnosis fall under class IIa if they are intended to image in vivo distribution of radiopharmaceuticals; active devices with functionality for diagnosis based on digital images fall in class IIa. [47]

Under the New Approach regulatory framework, a medical device is presumed to comply with the essential requirements if it meets the appropriate harmonized standards. The international standard EN/IEC 62304 on medical device software lifecycle processes (covering both software as a component of a medical device and standalone software) emerged as a global benchmark for evaluating software development. EN/ISO 13485 (quality management systems), EN/ISO 14971 (application of risk management), IEC 60601 (medical electrical equipment safety) and IEC 82304 (product safety standard for health software products) allow for the evaluation and control of design and development of medical software. [49-53]

Regardless of its risk classification, the developer/manufacturer wanting to affix the CE mark on his medical apps need to compile detailed technical documentation demonstrating that the app conforms to the essential requirements of the MDD, produce a declaration of conformity, affix the CE mark to the product and notify the Competent Authority of the respective Member State. As part of the technical documentation, app developers will also need to undertake a controlled test and risk assessment to demonstrate that their app supports and improves upon existing processes. [12] Additionally, manufacturers must ensure that the medical app complies with the communitarian and national data protection laws. [54]

The MDD and IVDD are currently undergoing revision with the intention that they will be recast as Regulations rather than Directives. After publication, expected in late 2016 or early 2017, there will be a three-year transition period, coming into effect in late 2019 or early 2020.
In general terms, the Medical Device Regulation (MDR) seeks to ensure the safety of medical devices by three means: by strengthening the pre-market conformity with essential requirements; by tightening vigilance once they are available (post-market surveillance); and by improving traceability throughout the supply chain.

4.2. Data Protection

mHealth solutions and devices can collect large amounts of information (e.g. data stored by the user on the device and data from different sensors), store and process it. The rising mHealth sector, particularly mobile apps, is changing the way significant amounts of health data is managed, shifting the paradigm from workstation systems located in the healthcare facilities to apps on smartphones and storage in shared cloud services. [55]

Mobile medical apps often rely on consumer data, including contact information, photos, and location. Through an interface called Application Programming Interface (API), app developers are able to continuously collect personal data, access contact data, send emails or SMS, record audio, use the camera and access stored pictures. APIs can also provide information about the device itself and about other installed apps as well as modify the global system settings. These data sources can be further processed, typically to provide some commercial revenue stream in ways unknown to the end user. [22, 56] Data can be collected and processed on the device or be transferred in real-time to third parties, via connection to an external API, without the knowledge of the user. [56] This raises concerns about the appropriate processing of data collected through apps by the various stakeholders in the app market – developers, publishers, health professionals, advertising companies, authorities and users. [3]

Google Play apps such as *Self-help Anxiety Management* and *iCardio* which provide, respectively, assistance with mental health concerns and activity monitoring, have access to user's personal data (symptoms, diseases and lifestyle habits). In fact, a recent study on security concerns of Android health-related apps exposed common shortcomings in security and privacy when communicating and storing health data. The authors stated that mHealth apps in Google Play commonly send sensitive personal data in clear text and store it on third party servers whose confidentiality rules may not be as robust as they need to be for the type of data being stored. [55]

Under EU law, there are special categories of personal data ("sensitive data") which, by their nature, may pose a risk to the data subjects when processed, demanding enhanced protection. These special categories include personal data revealing racial or ethnic origin; revealing political opinions, religious or other beliefs; and concerning health or sexual life. The processing of health data must therefore be allowed only with specific safeguards. [57, 58]

Users are concerned about the risks posed by the release of their health information such as unwanted sharing with third parties like employers or insurers. [38] 45% of users state they are concerned about the unwanted use of their data when using mobile devices for health-related activities. [59]. Moreover, loss or theft of devices storing sensitive information can be a serious security issue. By this means personal data could be accidentally exposed or easily leaked to unauthorized parties. This could be the case of both

healthcare professionals accessing health information from a mobile device or patients storing clinical data on a personal health record app alike. [3]

A Eurobarometer survey conducted in March 2015 asked 28,000 EU citizens what they think about the protection of their personal data. [60] According to the survey results:

- Approximately 70% of EU citizens are concerned about their personal information being used for a different purpose from the one it was collected for;
- Only 15% feel they have complete control over the information they provide online; one in three people (31%) think they have no control over it at all;
- Half of all European Internet users are worried about becoming a victim of fraud through the misuse of their personal information;
- Only 18% of respondents fully read privacy notices;
- Almost all Europeans say they would want to be informed, should their data be lost or stolen;
- Only 37% of Europeans are aware of a national public authority responsible for protecting their personal data rights;
- 90% of respondents think that it is important for them to have the same rights and protection over their personal information, regardless of the country in which the public authority or private company offering the service is based.

Personal data protection is a fundamental right in Europe, stated in Article 8 of the Charter of Fundamental Rights of the European Union, as well as in Article 16(1) of the Treaty on the Functioning of the European Union (TFEU). [22] The processing and storage of personal data concerning health is particularly sensitive. Appropriate data processing and compliance with personal data protection rules are therefore crucial for building trust in mHealth solutions. A clear legal framework applicable to the processing of personal health data on mobile medical apps is vital. This framework should anticipate any further processing such as using the collected data to build profiles and target users for commercial/advertising purposes. [22]

Between 1995 and April 2016, the processing and movement of personal data, including health data, within the European Union was regulated by the Data Protection Directive (officially Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data). [57] The data protection provisions are complemented by the e-Privacy Directive (officially, Directive 2002/58/EC concerning the processing of personal data and the protection of privacy in the electronic communications sector), which prescribes that consent and clear and comprehensive information to the user are necessary in order to place data on, and retrieve it from devices. [61]

Due to legal ambiguities and different transposition of Directive 95/46/EC into national laws, there are major differences between national data protection systems of EU Member States in regards to the use of personal data.

Having these shortcomings in mind and aiming to cope with the growing challenges of globalization, international data flows and rapid development of new technologies (e.g. mHealth), while ensuring that individuals effectively control their personal data, in January 2012, the European Commission proposed a comprehensive reform of the Personal Data Protection Directive. [57] After 4 years of debate and extensive revisions, the General Data Protection Regulation (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data) will supersede the Data Protection Directive and be enforceable on May 25, 2018. [54]

The fact that it is a "Regulation" instead of a "Directive" means it will be directly applicable to all EU Member States without a need for national implementing legislation, thus, providing for further harmonization of data protection rules in the EU.

As stated in the EC's *Green Paper on mHealth*, these new set of rules attempt to ensure legal certainty for businesses and increase trust on mHealth services with a consistent and high level of protection of individuals. [3]

4.3. Lack of Harmonized System Interoperability Standards

The results of the public consultation on mHealth published by the European Commission, highlighted the need for an EU mHealth interoperability framework. [3]

According to the International Organization for Standardization (ISO), interoperability is the "ability of independent systems to exchange information and to initiate actions on each other, aiming to work together for mutual benefit". [62] In general terms, interoperability refers to those properties of software that enable the exchange of data among systems in common formats, the use of common protocols, and ultimately the ability to work together. The main goal of interoperability in healthcare is to connect applications and data, so that they can be shared, distributed, always available and accessible by health professionals. [63]

Interoperability is a critical issue for mHealth because patients may have multiple clinical conditions simultaneously and thus interact with the health system via multiple points, providers, and professionals. Furthermore, the complexity and specialization of healthcare means that many diseases will require multiple professionals to be engaged in diagnosis, treatment and follow-up. [64, 65] For example, a patient who is diabetic, hypertensive, and suffering from depression is unlikely to use multiple, non-communicating, disease-specific monitoring apps.

The possibility of transferring data generated on mobile devices to electronic health records, healthcare providers or even from a provider to another raise multi-layered interoperability issues (i.e. semantic, technical, organizational and legal). [66]

To achieve interoperability, the developer must implement permanent structures and processes for continuous change management and co-operation among all players involved in the collection, storage and

processing of health data. [67] In regards to personal data protection, the security systems for wireless mHealth devices must support interoperability and must encrypt all data to allow for efficient and secure file sharing and storage. [68] Additionally, it is fundamental to use standards to govern health data concepts, patient identity, data processing protocols, and mechanisms for secure sharing of patient data that preserve confidentiality. The wide variety of terminologies and vocabularies required to describe and code health data coupled with the wide heterogeneity of health information systems in the Member States implemented by health authorities, hospitals, or doctors, make interoperability in mHealth a very complex task. [69]

Development of open standards (i.e. a set of software development formats and protocols for which information about its use and application is publicly available, with no fees for use and developed under a consensus process) is particularly critical for interoperability of mHealth solutions. The future of mHealth apps may be jeopardized if each app is developed with its own proprietary data format, management, and analysis, therefore impeding data-sharing with other apps and with electronic and personal health records. [2, 64, 69]

In this context, the standards for mHealth development are considered the main premises to ensure interoperability. For example, Health Level Seven (HL7) refers to a set of formats that specify the interfaces for electronic data exchange between heterogeneous computer applications in hospital environments and govern how healthcare digital systems exchange information with each other; the Systematized Nomenclature of Medicine-Clinical Terminology (SNOMED CT) is a coded taxonomy that can be used by health professionals, administrators and researchers in the medical area in order to improve the quality of healthcare delivery through an efficient and concise representation of clinical information (e.g., to define diseases, findings, procedures); the Digital Imaging and Communications in Medicine (DICOM), which defines structures for the exchange of medical images and related information, is the most used standard for medical images, achieving interoperability among different equipment and guaranteeing the availability of images. Despite these standards' potential to uniformly store data, supporting its processing and its automatic analysis, none of them is yet freely available for use. [62, 69]

4.4. Lack of High-Quality Evidence on Clinical Benefits

mHealth is currently not used to its full potential in the European healthcare systems. The need for high-quality evidence and robust data to support developer's claims in the mHealth field has been signaled in the European Commission *Green Paper on mHealth* as one of the possible causes. [3] Healthcare providers and potential payers need further evidence of mHealth's clinical and economic benefits before they scale up its adoption.

In accordance with financial forecasts, venture capital funding for mHealth initiatives has been growing in recent years. [15] However, scientific evidence's robustness has not been tracking the growing financial

support. Indeed, although the number of mHealth-related publications is growing gradually, the majority of the published evidence supporting its clinical use is limited to underpowered pilot data. [3]

Several recent meta-analyses and systematic reviews conclude that high-quality evidence for the use of mHealth is scarce. [14] In 2013, two systematic reviews of randomized clinical trials in mHealth addressed the use of such interventions to improve lifestyle behaviors, aid in disease self-management, and facilitate healthcare delivery processes. The researchers found that while many studies have been conducted, many are of poor quality and have a high risk of bias, and very few have found clinically significant benefits. On the other hand, these studies also showed some evidence suggesting benefits from specific mHealth applications, namely those helping patients quit smoking, improving HIV medication adherence, and modestly improving aspects of clinical diagnosis and management. Facing this mixed evidence for mHealth effectiveness, the authors stressed that high quality adequately powered trials are required to evaluate effects on objective outcomes and scale-up mHealth. [70, 71]

4.5. Lack of Reliable Content

The fast-paced growth of the healthcare app market has outpaced the ability to develop appropriate oversight and guidance for the clinical content of mHealth apps. [25, 72]

The sheer volume of mHealth apps available and the absence of a mechanism for verifying, certifying or ranking apps leaves providers and consumers with little to no information on app selection. The information these solutions provide can sometimes be insufficient as to who developed them and whether they have undergone appropriate reviews or followed established medical guidelines or clinical tests. [73] This environment is a key barrier to widespread physician adoption of mHealth apps, as he will be reluctant in prescribing mHealth apps given the unknowns about accuracy, efficacy, security as well as liability. [74]

A recent study on the reliability of medical apps specifically targeting patients suffering from colorectal diseases found that of a total of 63 colorectal themed apps surveyed, only 32% had medical professional involvement in their development or content. [12]

Pereira-Azevedo et al. reviewed Urology apps on PubMed, Apple's App Store and Google's Play Store with the aim of assessing the level of participation of healthcare professionals and scientific Urology associations in their development. The researchers found that one in five apps had no healthcare professional involvement (20.7%) and only a third had been developed with a scientific Urology association (34.7%). This study also demonstrated the lack of expert participation in the design of Urology apps, particularly those designed for the general public. [75]

Robson et al. urged caution when using melanoma risk analysis and detection apps due to their diagnostic inaccuracy. [76] Huckvale et al. performed a systematic review of existing asthma self-management apps (n=103) and concluded that none combined reliable medical information and appropriate supportive tools, and that some were even deemed unsafe for end-users. [77] In fact, while recent studies show growing

support for mHealth app use in patient monitoring and adherence to treatments, studies have also identified concerns around mHealth app content, accuracy and consistency. Higher level app functions such as calculating insulin dose, diagnosing illness or providing evidence based behavioral interventions have been found to be inaccurate in some instances and potentially harmful to consumers. [74, 78]

Content certification is required to improve accountability. Maintaining a certification scheme and a registry of certified apps or even issuing an official quality seal of approval could be reliable indicators of content credibility, app's effectiveness and user data safeguarding for healthcare professionals and patients. (69) Some app certification programs are already emerging. The company Happtique in the U.S. offers an app certification program based on operability, privacy, security, and content standards. The app is certified and sold on a specialized app store. [79] The UK National Health Service (NHS) has launched the Health App Library, a library of apps that have been endorsed for patients by the NHS and that can be prescribed by doctors. The submitted apps meet three minimum requirements: relevancy to people living in England; compliment with data protection laws; and compliment with trusted sources of information, such as NHS Choices. [79] The European Directory of Health Apps focus on increasing transparency of information about health apps. It gathers facts about 200 mHealth apps recommended by European patient groups and covering a wide range of health related topics such as medication reminders, disease management, exercise routines and physical impairment. [3] The Andalusian Agency for Healthcare Quality created the AppSaludable Distinctive, a seal which acknowledges mobile applications that are safe and reliable for users. The process is based mainly on self-assessment and subsequent evaluation by an expert committee of the Agency. [74, 79] Companies like HealthTap in the US are also getting involved in the app evaluation market, with an application called AppRx, which enables physicians in the network to review health and medical apps based on app's usefulness, reliability of content and usability. Since 2013, the app has a new feature that enables around 100,000 medical doctors in the network to recommend high-quality medical mobile apps to everyday users, allowing them to make more informed decisions on the vast landscape of health and wellness apps. [80]

4.6. Need of a Mindset Shift and Adequate Infrastructures

The shift towards patient-centered care may require the re-design of existing infrastructures and healthcare organizations, currently centered in healthcare services and professionals. According to Research2Guidance's *mHealth App Developer Economics 2014* study, the resistant mindset of healthcare professionals to move the focus of healthcare from services to patients is still an important barrier to overcome. [81]
Introducing mHealth services may require preliminary training of healthcare staff in order to adapt and develop their digital skills. [3] Clinicians and healthcare providers will not readily embrace the new but somehow challenging changes that mHealth solutions bring into practice.

mHealth strongly depends on high capacity, ubiquitous and flexible networks. In this context, the European Commission recently adopted a legislative package for a "*Connected Continent: Building a Telecoms Single Market*", which recognizes the need of high-speed and high-quality networks, while aiming at a greater degree of harmonization and more investment within the single market. Also, under Horizon 2020, the European Commission will provide funding for mHealth and intends to support digital health literacy of healthcare professionals and citizens as it is key to ensuring that mHealth contributes to equal access to healthcare. [3]

4.7. Reimbursement and Lack of Economic Incentives

As stated in the *Green Paper on Mobile Health* issued by the European Commission, a major obstacle preventing mHealth from reaching the mainstream of healthcare provision is the lack of innovative and appropriate reimbursement or funding schemes able to cover for patient's costs with mHealth solutions and associated devices. [3] Furthermore, if unclear reimbursement mechanisms are in place, there is reduced incentive for application developers to focus on healthcare services as a customer. [82] Stakeholders who responded to the Public Consultation on this Green Paper see reimbursement and funding as key to the future of mHealth in Europe. In the Summary Report released by the European Commission on January 2015, the respondents called for increased state/insurance funding or reimbursement of mHealth. [83]

Delivery of healthcare and the setting up of payment/reimbursement schemes is the responsibility of individual EU Member States. The scope of action of the European Commission within this matter is quite limited. At the national level, many health systems have no defined model for pricing and reimbursement of mHealth initiatives. Whereas some EU Member States are more advanced in enabling the use of remote care solutions (e.g. Denmark), in other Member States national law still defines medical care based on the actual physical presence of patient and doctor, preventing reimbursement of mobile and remote healthcare solutions. [3, 82]

Currently, very few examples of implemented funding models for mHealth services exist in the EU. Payer and provider are both important variables in the healthcare delivery equation but patients are increasingly becoming the primary factor determining what is valuable and should be paid for. At present there are some reimbursement pilot schemes initiated by different stakeholders (including insurers) but these are still small-scale projects. [84] Other models leave to institutional payers and national authorities the choice about which mHealth solutions can be included into the nomenclature of reimbursable healthcare activities. To be reimbursable, a mobile health solution must undergo a Health Technology Assessment (HTA) and demonstrate at least equivalent effectiveness compared to the standard clinical care as well as proof of a positive risk-benefit ratio and efficacy. [82]

5. DISCUSSION

5.1. REGULATION

The European Commission's eHealth Action Plan 2012-2020 underlines the potential of mHealth for patients, including mobile medical applications, and the need to have a clear regulatory framework to ensure its development and safe adoption. [3]
Recognizing that mobile health has too much potential to allow regulatory issues to undermine it, and that these technologies are already present in many sectors and becoming increasingly common to be used to provide healthcare, policymakers are working to implement reforms that will protect consumers without impeding innovation and economic progress. In doing so, policymakers should keep in mind that legislation needs to evolve over time accommodating rapid changes in markets, technologies and business models, while keeping the regulatory objectives stable and ensuring sufficient regulatory confidence for companies.

The 2007 revision of the regulatory framework explicitly brought software – including applications – into the regulatory scope and definitions. Guidance (e.g. MEDDEV 2.1/6 on stand-alone software) exists to determine whether a given application is intended to be used specifically for diagnostic and/or therapeutic purposes. However, several regulatory barriers to a mainstream adoption of mHealth (particularly of mobile medical apps) still exist. Below is discussed the effect of legislation uncertainty and to what extent this uncertainty can be tackled by the future Medical Device Regulation (MDR). [46]

5.1.1. Limited scope of European Commission's competence

The European Commission's Green Paper on mHealth was intended to initiate broad stakeholder engagement and address the barriers to mHealth deployment. [14] The Green Paper poses 23 questions in 11 wide range policy areas. Although this was a good effort, under the current Lisbon Treaty national provision of healthcare, including mHealth deployment, is outside the scope of EC competence. [3] This makes mHealth a very sensitive political area for the European Commission that must prevent stifling the competence of national authorities/governments.

5.1.2. Lack of regulatory harmonization

Due to different transposition of the "New Approach" Directives on medical devices into national laws, the EU regulatory landscape is too fragmented as it is largely dominated by individual State jurisdictions. [39]

Consequently, manufacturers are essentially confronted by national legal obligations, compromising the single market and a broadly adoption of mHealth solutions. Additionally, current EU national laws and regulations don't provide a definition of mHealth, which often hampers an in-depth analysis of these new medical solutions. [85] To accelerate mHealth adoption, harmonization of regulations on a Europe-wide basis is crucial.

5.1.3. Borderline products, "intended purpose" and "accessory"

The way in which an app or device is regulated directly influences the manufacturer's business model. If an app falls under the definition of a medical device, it must adhere to medical device regulations, as well as to onerous validation and testing requirements. Uncertainty in the regulatory framework can dampen the growth of mHealth.

The 2014 European Commission's Green Paper on mHealth recognized that "in the EU, there are no binding rules as to the delimitation between lifestyle and well-being apps and a medical device or in vitro diagnostic medical device". [3]

The central challenge in evaluating the intended use of a mobile app arises from the way the use of health-related products is deeply tangled with wellness, which can be difficult to distinguish from a medical purpose. At what point does a product cease serving a wellness/wellbeing function and starts serving a medical purpose? For instance, when does a weight management product cross the line from assisting in general health conditioning to preventing or treating obesity? To what extent can the manufacturer appoint the benefits of weight management to overall health without suggesting the product is intended for a medical purpose?

In fact, the distinction between mobile medical apps and mobile lifestyle and wellbeing apps can become unclear as healthcare models become more patient-centric. Some mHealth solutions, such as health and fitness apps, are intended to support general consumer wellness. However, if integrated in a diagnosis and treatment schedule, could be classified as medical devices. [86]

The grey area between wellness and medical purpose creates significant uncertainty to app developers as to whether a given product in a given context will be deemed to have the intended use that falls under the medical device regulatory framework. [87]

It is still unclear if and to what extent lifestyle and wellbeing apps could pose a risk to citizen's health. Clarity is required as to the rules that borderline lifestyle and wellbeing apps must comply.

In the specific case of mobile medical apps, current legislation poses the problem of evaluating the "intended purpose". For example, would a smartphone be considered a medical device if the smartphone's manufacturer also sells medical device software to run on the phone or if a third-party medical software app is sold through the smartphone manufacturer's online app store? Further clarity is needed in evaluating the intended purpose of a mobile app.

Another fundamental regulatory challenge is determining the scope of the "accessory" definition. In a dynamic and rapidly developing technological landscape, the boundaries between accessories and stand-alone devices are not always clear and may lead to regulatory requirements that are incongruent with the product's risk level. Indeed, if the current "accessory" definition was applied equally across the spectrum of mobile and wireless-enabled medical devices, mobile phones, entire cellular networks, and even the Internet itself, could potentially be considered accessories to a medical device.

Considering the example of a smartphone used to transmit data from a medical device connected to a patient to the physician, is the smartphone an "accessory" to the medical device if the phone manufacturer promotes or intends for the phone to be used as part of a mHealth system? Is the manufacturer of the smartphone responsible for reporting any adverse events associated for example with a service loss? Further, if the smartphone is part of a mHealth system involving Class III medical devices, shall it be regulated as a high-risk Class III medical device?

The lack of clarity concerning the qualification as an accessory to a regulated medical device can potentially stifle the widespread access and usability of mobile medical apps.

5.1.4. Notified Bodies

As described, for a medical device to access the EU market, manufacturers must follow a conformity assessment and, with the exception of low risk class I devices, undergo an inspection and certification procedure carried out by a Notified Body.

Taking into account that mHealth devices, particularly mobile medical apps, can be of a very different and new nature compared to "traditional" medical devices, it is essential that Notified Bodies have the solid knowledge and expertise to be able to assess a mobile medical app properly while keeping pace with the rapid development of these kind of technologies.

5.1.5. Regulatory status

Clarity on the regulatory status is important for users. End users should be aware of the level of scrutiny that a mobile health solution and its components have been subject to in order to access its fitness for purpose. The responsibility of ensuring this clarity on regulatory status lies with the manufacturer. The current regulatory framework requires for devices to have an appropriate level of traceability and post market surveillance to ensure safety is maintained through the product lifecycle. [86] However, a large number of apps are available on app distribution sites, regardless of their legal classification as medical devices, making it clear that market surveillance and enforcement by competent authorities is quite limited. [12]

Before placing a medical device on the market, manufacturers are required to register with their Competent Authority. However, at the present, there is no central European register for manufacturers or medical devices which means, in practice, that if a patient wants to verify whether a device or manufacturer is registered, he would have to enquire with each Competent Authority for the 28 Member States.

5.1.6. Software lifecycle and regulation

There are specific aspects of the software lifecycle challenging the conciliation of the EU regulatory process with the unique characteristics of mobile software. The current regulatory framework was published long before these technologies existed and built for medical devices with a very different development cycle when compared to software.

Even if applied consistently, the medical device regulatory process is not fully adaptable to mobile health software. The time required to receive Notified Body's clearance may be the first roadblock. According to information published by the Notified Body Emergo Group, the assessment and approval timeline to get regulatory approval and affix the CE marking can vary from 3 to 5 months for a Class I device with a measuring function and from 6 to 9 months for a class III medical device. [88] Medical technology products typically have a lifecycle of only 18-24 months before an improved product becomes available. This period is significantly smaller for stand-alone software. Consequently, app developers need to shorten time to market as much as possible.

It is important to address what happens to an app regulatory status when the software is updated. Does the application have to go through the entire conformity assessment procedures again?

In accordance with the MDD, when a Notified Body is involved in the conformity assessment of a medical device, he must be informed by the manufacturer of any plan for substantial changes to either the quality system or the device. Surprisingly, it is up to the manufacturer to decide if a change is substantial. For a Class III high-risk device, the Notified Body must be informed about every change to the approved design. The Notified Body must assess the changes proposed and verify whether the quality system and the product itself still meet the essential requirements.

In a dynamic and rapidly changing environment, developers of mobile medical applications cannot engage in iterative conformity assessment submissions to the Notified Body to maintain their device's compliance. Clearer guidance is needed to assess what constitutes a "substantial change" requiring a supplemental evaluation by the Notified Body.

As stated in Meddev 2.1/6, most computer programs used in healthcare have applications which consist of both medical device and non-medical device modules and platforms. [47] As an example, if an app is purely a record archiving and retrieval system, it is unlikely to be considered a medical device; however, if it includes

a module that interprets data or performs some calculation, then it is expected that this particular component may be considered a medical device. The modules with an intended medical purpose must comply with the requirements of the medical device Directives and must bear the CE marking. The non-medical device modules are not subject to the requirements for medical devices. Again, it is the obligation of the manufacturer to identify the boundaries and the interfaces of the different modules. [47]

For efficiency, cost-saving and marketing purposes, app developers often release a beta version of an application before releasing it to the general public. Advanced users can help troubleshoot final problems on design or functionality. [6] Given the risky nature of this practice in the context of healthcare, greater regulatory clarity is fundamental, while having in mind that not allowing beta testing of mobile medical applications makes competition with other digital applications more difficult for mobile medical apps' developers.

5.1.7. Medical Device Directives Recast

As the European marketplace for mobile applications continues to develop, regulatory predictability and certainty is vital. A clarification and harmonization of the existing regulatory framework is paramount. The current revision of the EU regulatory framework on medical devices offers an important opportunity in this respect.

The MDD and IVDD are currently undergoing revision and recasting as Regulations rather than Directives. As Regulations, they will no longer need to be transposed into the national laws of the Member States and they will be applied straightforwardly, fostering harmonization across all EU countries. After publication, expected in late 2016 or early 2017, there will be a three-year transition period, coming into effect in late 2019 or early 2020.

Medical device qualification and classification will continue to be the rule against which all medical devices are measured for safety and performance, including mHealth apps. However, the proposed Medical Device Regulation (MDR) differs in several important ways from the EU's current Directives.

Although the general nature of the CE marking conformity assessment procedures will not change, the processes involved will be considerably more stringent with a higher burden of evidence required to demonstrate conformity to the MDR's requirements. Greater emphasis will be placed on clinical data and clinical evaluation. Equivalence, currently used to justify referencing to studies performed with other devices already CE-marked, will be more rigorously interpreted making it far more challenging to demonstrate clinical safety or performance for lower risk medical devices. The MDR proposal will also make Post-Market Clinical Follow-up (PMCF) mandatory as part of the ongoing assessment of potential safety risks. At this point it is safe to say that requirements for clinical evidence will increase substantially and will require significantly higher investment from companies.

The definition of medical device and active implantable medical device covered by the MDD will be expanded to include devices that may not have a medical intended purpose, such as colored contact lenses and cosmetic implant devices and materials. Also expected to be included in the scope of the regulation are devices designed for the purpose of "prediction" of a disease or other health condition. Software will still be considered an active device; the term "stand-alone software" will be replaced by "software that are devices in themselves" or "independent of any other device". Additionally, the definition of accessory is expanded to "assist" and not just "enable" a device to be used, thus, broadening the number of products which could be classified as accessories to medical devices.
The classification criteria (Annex VII) proposed by the European Commission in the MDR includes 23 rules. A new rule is introduced – currently Rule 10a – for classification of software. In accordance with the potential risk posed to the end user, software can fall under all risk classes. IVDs will be reclassified to four risk-based classes - Class A, B, C and D – with more stringent conformity assessments. Consequently, some types of devices that are currently self-assessed by the manufacturer will require the involvement of a Notified Body in their CE Marking after the MDR comes into effect.

The proposed regulation aims to clarify and strengthen the powers of Notified Bodies, who will be required to certify various aspects of medium and high-risk devices before they enter the market and to check their safety and performance once they are on the market. New rules allow the Notified Bodies to carry out unannounced inspections of manufacturing sites and make physical and laboratory tests on devices. Notified Bodies are already signaling they will not be able to process all this extra work, which may lead to compliant devices losing access to the European market and further enhancing barriers to adoption. [89]

Compared to the MDD, the MDR promotes a shift from the pre-approval stage (i.e. the path to CE Marking) to a life-cycle approach. The MDR will grant Notified Bodies increased post-market surveillance authority. Unannounced audits, product sample checks and testing will strengthen the EU's enforcement regime and help to reduce risks from unsafe devices. Annual safety and performance reporting by device manufacturers will also be required in many cases. Additionally, the proposed MDR mandates the use of unique device identification (UDI) mechanisms. This is expected to increase the ability of manufacturers and Authorities to trace specific devices through the supply chain, and to facilitate the prompt and efficient recall of medical devices that have been found to present a safety risk.

Device manufacturers will be required to identify at least one person within their organization who will be in charge of ensuring compliance with the requirements of the MDR. The organization must document the relevant qualifications of this individual relative to the required tasks. This requirement will apply to all companies no matter what their size (the only exception being for manufacturers of custom-made devices who are micro-enterprises, i.e. business employing nine people or fewer). However, the MDR is not explicit

about whether the person must be employed or can be a consultant, nor is the regulation specific about whether the person must be available full-time.

The central database on medical devices is expected to be expanded to create an improved system for all relevant information, covering economic operators, notified bodies, market surveillance, vigilance, clinical investigations and certificates. It will provide patients, healthcare professionals and the general public with comprehensive information on medical devices available in the EU, enabling them to make better informed decisions.

It is also important to analyze the reason why, despite the fact that developers/manufacturers have valid sources of information regarding mobile medical apps-related legislation, they do not integrate them in the development and lifecycle of their products.

One of the reasons may be that it is not easy for developers to interpret specific laws, directives and definitions and apply them into their daily practice. Interestingly, the mobile apps' market is dominated by individuals or small companies, with 30% of mobile app developer companies being individuals and 34.3% being small companies (defined as having 2-9 employees). [3] These small teams, often without a comprehensive understanding of the regulatory framework, find difficulties in managing and controlling documentation without losing productivity. Creating and maintaining traceability between records and cost-effective change management is considered arduous and time consuming as well as tracking risk and implementing preventive and corrective actions is considered a large burden. [5]

In these situations, mHealth companies may find themselves ill-prepared to meet developing regulatory challenges. Compliance with regulations may be perceived as a barrier to usability and as a slowdown on a timely access to market. This is arguably the most serious obstacle for small mHealth entrepreneurs to enter the healthcare market and grow their businesses.

The complexity and rate of change of software, both embedded and stand-alone, are rapidly outpacing the ability of organizations to address these issues with manual processes and disconnected point tools. In this context, the EU-wide adoption of already available global standards and specifications will be key in creating better market entry conditions. It is recommended that companies venturing into the mHealth area invest at the early stages in developing a strong understanding of the legal and regulatory issues, associated investments and timelines, before developing the technology or making improvements to an existing one. Such companies must plan to invest in the infrastructure and processes necessary to ensure that regulated mHealth apps remain compliant. A coherent and integrated commercial strategy for the development of devices relevant to mHealth should be considered from a worldwide scope.

5.2. DATA PROTECTION

It has been 21 years since the current data protection rules were adopted. New ways of delivering healthcare such as mHealth and in particular mobile medical apps, have profoundly changed the way patients and healthcare professionals store and share health information. In this fast-changing environment, the individual's fundamental right of effective control over his own health data must be safeguarded.

5.2.1. Lack of transparency

The public consultation on the European Commission's Green Paper on mHealth identified "safety and transparency of information" as one of the main issues for mHealth deployment. Respondents considered that having users consent as well as strong privacy and security tools in place is crucial for mobile health apps.[3]

Many apps do not have a privacy policy and fail to be transparent on informing the user in a meaningful way about the type of personal data the app may collect and process, and for what purposes. As reported by a 2012 study on mobile apps' privacy, just 61.3% of the top 150 apps in the market provided a privacy policy. [90] Additionally, many apps collect data from smartphones, without any meaningful relationship to the known functionality of the app and are not transparent about the duration of the processing. [22, 90]

Under the Data Protection Directive, personal data may only be processed for fair and lawful purposes and these purposes must be defined before the data processing takes place (purpose limitation). In order to prevent unnecessary and potentially unlawful data processing, app developers must carefully consider which data are strictly necessary to perform the desired functionality (data minimization). [22]

Comparing this approach with the new GDPR, data controllers (the ones determining the purposes and means of the processing of personal data) must continue to provide transparent and fair information on data processing to end users of mobile medical apps as well as continue to comply with the principles of purpose limitation and data minimization. However, as the requirements in the GDPR are more detailed than those in the current Directive, existing forms of data processing notice will have to be reviewed and updated, for example, to be more comprehensive and to verify if the user is being informed in a clear and accessible way, if the right to withdraw consent at any time without detriment or the period for which the data will be stored are clearly stated. [54] Here it is critical to achieve the appropriate balance between providing information and avoiding 'notice fatigue' (where people ignore notices or warnings because of over-exposure). [91]

Under Articles 37-39 of the GDPR, for public authorities or companies whose core activities consist of processing on a large scale special categories of data, a new player is added to the equation - the Data Protection Officer - in whom the responsibility of ensure internal compliance with the GDPR obligations

within these organizations is delegated. This will be the case of mobile medical app developers that process health data of, for example, more than 5000 users within 12 months, where a DPO must be employed or service contracted. [54] Faced with this requirement, many app developers will have to contract a DPO, which will certainly have a financial impact on the business. The GDPR requires that all companies that process personal data concerning health and/or engage in profiling/monitoring of data subjects conduct a Privacy Impact Assessment (PIA) prior to the processing. As an overview, this assessment includes a systematic description of the foreseen processing operations and their purposes as well as the measures envisaged to address the security risks, ensure the protection of personal data and demonstrate compliance with the GDPR. [54] Taking into account that profiling is what makes the use of personal data in healthcare relevant (for example, to be able to monitor a patient over time), the PIA will always be needed for mobile medical apps. In fact, what should be limited in marketing and social media, we want to promote in healthcare - monitoring, profiling, further processing and traceability. Additionally, the user must be informed of profiling details in advance and explicit informed consent for that profiling must be obtained prior to initiation of profiling procedures. [54] These additional requirements and the potential fines for doing it wrong, will be time-costly and will require significant investment from mobile medical apps developers which intended purpose involves profiling of health data.

The user of a mobile app must understand what an app intends to do before he can give valid consent for the collection and processing of health data. Once the app is downloaded, consent is often reduced to a screen containing a single “Yes I accept” option of the terms and conditions in order to finish the installation. [22] Consent must be explicit and specific for sensitive data which would not be achievable by the general means used by app developers - simply clicking an “install” option. This kind of expression of will cannot be considered a valid consent, because it does not specify the particular data item/category to be processed. Thus, the user must be free to accept or refuse the processing of his personal data by means of an option to “cancel’” or otherwise stop the installation; consent must be sought for each type of data the app intends to access and these data must only be accessed when the app is being used for its intended purpose. [55, 92] Additionally, the user must have this necessary information at his disposal, before any personal data is processed (including data processing during installation), in order to decide in an informed and accurate way. A general and lengthy set of terms and conditions/privacy policy without a precise indication of the aim of the processing to which the data is subject cannot comply with the imperative need of a specific and explicit consent. “Special categories of data” or “sensitive data” are retained by the GDPR and extended to cover genetic and biometric data. As with the current Data Protection Directive, processing of such data is subject to more stringent conditions than other forms of personal data.

In general, comparing with the current legislation, the conditions for obtaining consent for health data processing have become stricter. Where Directive 95/46/EC allows controllers to rely on implicit and inactive

("opt-out") consent in some circumstances, the GDPR requires consent to be unambiguous and not to be assumed from inaction. Instead, the user must signal agreement by "a statement or a clear affirmative action". Silence, pre-ticked boxes or inactivity is presumed inadequate to affirm consent.
Also, consent must be provided in an intelligible and easily accessible form, using clear and plain language and be as easy to withdraw as to give, in a simple and effective manner. For consent to be informed, the data subject should be aware, at least, of the controller's identification and the purposes of the processing for which the personal data are intended. [54, 57] More importantly, under the GDPR, consent is deemed invalid "where there is a clear imbalance between the data subject and the controller". This additional requirement can be troublesome for manufacturers of mobile medical apps that entail provision of services to healthcare providers. As an example, when a medical doctor prescribes the use of an app for remote patient monitoring, the patient will mostly not feel in a position to refuse it, regardless of the patient ticking all the consent boxes in the app. In this case, consent would likely have been obtained in a case of imbalance and, therefore, be invalid. The imbalance criterion between healthcare provider/institution and the patient may also play an important role in clinical research. About consent withdrawal, Article 7(3) of the GDPR gives users the right to withdraw consent at any time in a manner as simple as it was given. Additionally, users must be informed of the right to withdraw before consent is given. Once consent is withdrawn, users have the right to uninstall the app and have their personal data erased and no longer used for processing, the so-called "right to be forgotten". Where personal data is processed for direct marketing the user must be explicitly informed of that fact and will have a right to object. [54]

It is expected that many data protection notices will need to be subject to a gap analysis and amended. Although many companies have already adopted privacy processes and procedures consistent with the Directive, the GDPR, as discussed, contains time consuming and potentially onerous new protections for EU app users and threatens significant fines and penalties – up to 4% of worldwide annual turnover or €20 million, whichever is greater - for non-compliant data controllers and processors once it comes into force in May of 2018. Notably, companies outside of Europe, such as those in the US who offer mobile medical apps to European citizens, will fall under the scope of this legislation and will face the same penalties for non-compliance. [54]

In order to promote trust on mHealth solutions and foster transparency, the European Commission's proposed to draw up an industry-led Code of Conduct on mobile health apps, covering the topics of privacy and security. The possibility of drawing up codes of conduct is foreseen in Article 27 of the Data Protection Directive and this possibility continues to exist under the GDPR. [93] The objective of this code is to foster citizens' trust in mHealth apps, raise awareness of and facilitate compliance with EU data protection rules for app developers, particularly, for SMEs and individual developers who may not have access to legal expertise. On 7 June 2016, the Code of Conduct has been formally submitted for comments to the Article 29 Data Protection Working Party, an independent EU advisory group. If followed by app developers, the Code of

Conduct can answer the majority of concerns on privacy and security of mobile apps. In accordance with the draft of this Code, user's consent must be free, specific, informed and explicit when obtained for the processing of health data; withdrawal of consent has to result in the deletion of the user's personal data; only data that are strictly necessary for the functionality of the app may be processed and only for specific and legitimate purposes (purpose limitation and data minimization); privacy considerations have to be included at each step of the apps' development (privacy by design) and wherever the user is given a choice the app developer has to pre-select the least privacy invasive choice by default (privacy by default); the user has the right to access his personal data, to request corrections and to object to further processing; personal data may not be stored longer than strictly necessary; the appropriate measures must be implemented to ensure the confidentiality, integrity and availability of the personal data processed and to protect against accidental or unlawful destruction, loss, alteration, disclosure, access or other unlawful forms of processing; any processing for secondary purposes needs to be compatible with the original purpose; the user must be informed prior to data disclosure to third parties and there must be an agreement in place between the app developer and the third party; data transfers to a location outside the EU/EEA, need to be supported by an adequacy decision of the European Commission; and the Code provides a checklist to follow in case of a personal data breach. Additionally, it includes two annexes: a Privacy Impact Assessment (PIA) which is intended to help app developers determine whether they have respected the main requirements of the Code, and whether they have followed good privacy practices before making the app available; and an example of an information notice. [94] Once approved, the Code will be applied in practice: app developers can sign it on a voluntary basis, thereby committing to following its rules and having their apps included in a publicly available register. [93] The emergence of codes of conduct and guidelines is crucial to maximize transparency and boost trust and confidence on personal data protection in the mHealth context.

5.2.2. Poor security measures

In mobile apps which collect and store large amounts of health data, if there is a personal data breach, unauthorized processing of sensitive data may occur. [22] This vulnerability increases as mobile medical apps become more connected to hospitals, insurance providers, and other medical devices. For instance, special privacy and confidentiality issues involving family planning services and treatment for sexually transmitted diseases can raise important privacy implications. A 2015 examination of the 600 most commonly used mHealth apps revealed that only 30.5% had a privacy policy and adequate security measures in place. [85]

Under the GDPR, to prevent privacy and confidentiality issues, data controllers must implement, as appropriate to the risk involved with the data processing, pseudonymization (privacy-enhancing measures that aim to reduce the risk of singling out one individual in a data pool, not included in the current legislation), encryption, redundancy, regular penetration tests and intrusion detection measures, along with a continuous

process for evaluating the effectiveness of the implemented measures. [54] Thus, in order to comply with their respective security obligations as data controllers, app developers, app stores, operating systems/device manufacturers and third parties have to implement an ongoing assessment of both existing and future data protection risks and evaluate effective mitigating measures. [22, 57]

The GDPR provides that each European company/institution dealing with the processing of personal data must appoint at least one person as a Data Protection Officer (DPO). This person will ensure, in an independent manner, the internal application of the provisions of the Regulation. [54] Under Article 31, the DPO will be under a legal obligation to notify the Supervisory Data Protection Authority without undue delay, but in any event in less than 72 hours after becoming aware of the breach (unless a delay can be duly justified). This includes "accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed". Individual users have to be notified if adverse impact on their interests and rights is determined (Article 32). In this way, companies processing personal data must re-examine their processes and procedures in order to ensure compliance and enhance their security measures.

In a related topic, under Article 18(1), the GDPR creates a new right to data portability that allows users to export health data from one company/provider to another. The data must be made available in a structured, commonly used, machine-readable and interoperable format. [54] This requirement will have a great impact in the designing of mobile medical applications, especially those working directly with patient electronic health records. By 25 May 2018 all existing systems must be adapted for data portability. Companies that are currently designing systems should do a gap assessment to see if their design complies with data portability requirements. This could be particularly troublesome, since the GDPR does not impose an obligation of developers to maintain technically interoperable systems. Thus, there is some uncertainty whether the format must be interoperable, or whether this is a matter of best practice which controllers are encouraged to adopt. Additionally, the personal data which are being ported may relate to more than one individual and, as a principle, portability of data should not breach the data protection rights of others. It is not clear how a developer would be expected to make this assessment.

In this context, surprising results were found by the cyber security insurer Lloyd's in its report released in September 2016 on a survey of 346 senior decision-makers at large businesses across Europe, which deal with personal data collection and processing. This survey analyzed how business leaders are approaching the challenge of cyber security and what they are doing to ensure their organizations are ready for the implementation of the GDPR and well prepared in the event of a data breach. [95] According to this report, 92% of respondents said their company had suffered a data breach in the past five years, yet only 42% are worried about suffering another breach in the future; and 97% of respondents have heard of the GDPR but only 7% said they know "a great deal" about it; 57% said they know "little" or "nothing" about the new regulation, despite the serious financial and legal consequences of not complying with its rules. [95]

5.3. INTEROPERABILITY

The absence of standards that mandate system interoperability between mHealth solutions and devices results in software incapacity to exchange data with other applications or systems. This prevents mHealth investments from being well used and limits the scalability of such solutions. [3] The development of an open standard that mandates interoperability is a key factor in the adoption of mHealth by healthcare providers, patients and payers. The slow uptake of international interoperability standards is even more problematic for the app market as it is dominated by SMEs and individual app developers, who may not necessarily have resources for legal advice or knowledge of multi-layered standardization activities. [3, 23, 56] Consequently, they may favor short-term strategies for quick market access.

There is a need for the European Commission to develop and certify open standards for the development of mHealth solutions. Providentially, the European Commission's eHealth Action Plan 2012-2020 focuses on developing common standards to enhance interoperable healthcare systems among Member States. [63, 96] A first step towards the setting-up of such common interoperability frameworks has been the adoption of the guidelines on minimum patient summary dataset to be shared across borders by the eHealth Network of Member States in November 2013. [3, 28] Given that these standards are optional for app developers, a system of financial incentives could help make interoperability a reality and contribute to a faster adoption of mHealth solutions.

5.4. EVIDENCE

The majority of studies published on mHealth discuss app usage, not app effectiveness in terms of improving health outcomes or lowering healthcare costs. There are few cost-effectiveness analyses with respect to mobile technology as a modality for health promotion or risk reduction. [74] Clinical trials to assess when, where, and for whom mHealth devices, apps, and systems are effective are paramount to clarify the real potential of these technologies and support its clinical use and integration within treatment protocols.
Randomized control trials (RCTs) are still the "gold standard" for generating evidence regarding the effectiveness of new interventions. However, designing trials around nonstandard systems of care, like mHealth, adds a layer of substantial complexity. Classical scientific practices, like RCTs, present a number of challenges for mHealth innovators and may not be suitable to generate clinical evidence. First, RCTs can be expensive, both in terms of time as well as money, which can prohibit smaller mHealth innovators from performing them. An RCT may take years to complete and may not even be feasible due to the rapid pace of technological innovation both for apps and the mobile device they run on. Furthermore, many mHealth interventions lack control groups and very few have designs and organizational structures that facilitate this type of evaluation. [97] Some researchers have suggested that complex interventions like mHealth require a

broader definition of what may constitute “evidence” in this fast-moving field. [71] In this context, focusing exclusively on randomized trials for evaluating interventions may be too restrictive for mHealth. While the first priority should be creating a primary evidence base by studying apps in well-controlled studies, the pace of science is incongruent with that of the mHealth app’s business sector and consumer demand. This could explain why there is so far only little evidence for the clinical benefit and cost-reducing potential of health apps.

5.5. CONTENT

App developers typically have little health-related expertise. It is important that they partner with recognized experts and content providers to ensure current, accurate, and trusted information in the desired format.

The proliferation of mHealth apps increases the need for appropriate rating and certification mechanisms. Lack of oversight and content verification is hindering the selection and differentiation process of reliable mobile apps from those that are inaccurate or even fraudulent. [75] In order to ensure sufficient reliability on apps’ content, maintaining a certification scheme and a registry of certified apps or even issuing an official quality seal of approval should be envisaged. Apps’ content should undergo a strict scientific review based on generally accepted evaluation criteria and led by healthcare professionals. This type of certification process could be reliable indicators of content credibility and app’s effectiveness and ensure these applications can be trusted by users.

The ultimate goal of app’s certification schemes is indeed to help patients, healthcare providers and/or healthcare organizations feel confident about their app selections in terms of usability, functionality, content’s accuracy and evidence base support. Despite mHealth apps’ reviews being reliant on proprietary evaluation methods used by each certification organization, certification mechanisms create easily searchable repositories, grounded on systematic evaluations and continued updating as new apps become available. [79]

However, reviewing apps can be resource intensive and time consuming so app listings may not reflect the range of available apps on the market at a given time. For example, UK’s NHS Apps Library was launched in March 2013 with 70 apps. One year later it listed 30 more apps, which is few compared to the thousands of apps that were commercially available and each year arrive to the market. [79] The evaluation and certification process can also be subject to error. *Happtique* recently suspended their app certification program when independent groups found security flaws in apps that *Happtique* had “certified” as secure. [79] In fact, the most important evidence often comes from users themselves. Although user ratings are generally not focused on the accuracy of the information or the evidence base supporting the app, they can be helpful in determining usability and functionality. [64, 79]

5.6. FITTING mHEALTH INTO EXISTING SYSTEMS

Workflows and practices must be transformed to enable the revolutionary outcomes resulting from technological innovation. Clinicians and healthcare providers should study how services can be altered to better accommodate these new technologies, instead of attempting to fit these disruptive technologies into existing systems, which has historically been shown to prevent many of the expected gains. [14] Healthcare systems must open-up to the possibility of receiving data from patients (e.g. collected by mobile apps) and ensuring ubiquitous access to care. This implies a change in the role of professionals who may have to remotely monitor and interact with patients. [3]

Healthcare professionals are often reluctant to engage with technology partly due to the scale and pace of its development. Lack of education and training compromises the health professional's confidence to use new or improved technology in clinical settings. They also express relevant concerns about quality, reliability, privacy and security of some mHealth technologic solutions. [35]

In this context, adaptation of healthcare workflows and practices to a more patient-centric delivery of care as well as training and education of both healthcare professionals and patients/users can play a big role in a mainstream adoption of mHealth.

5.7. REIMBURSEMENT

Reimbursement is a key factor in the distribution of mHealth services over the EU. Reimbursement systems try to align incentives between health payers and health providers to deliver the most appropriate care to patients in the most cost effective way. Key issues remain over whether and how users pay for the mHealth solutions and how to incentivize healthcare professionals to use and prescribe them. As the principal bearers of health costs, payers—both governmental agencies and private insurers—should have an interest in helping consumers adopt healthier lifestyles and in promoting more value-conscious healthcare. [28]

There is no proven model for reimbursement of mobile health apps. [3, 74] One possible option is to follow the current mobile apps model and require users to self-pay via the app stores. However, prescription-based download is not yet supported in the app stores.

Cases are emerging where a partner can pay directly for these apps (e.g. a pharmaceutical company) in the context of an existing therapy. For example, myVisionTrack has worked closely with a large pharmaceutical company in clinical trials. The partner may provide the app to the user for free and reimburse myVisionTrack directly. [98]

In general, current reimbursement models are based on the number of assessments per patient performed by a healthcare professional. While empowering patients to manage their own disease with remote monitoring from their physician, mHealth significantly changed this paradigm, resulting in less need for

physical assessments and more remote digital support. Hospitals and health professionals are often afraid to lose revenue if their patients pay them fewer visits. As a result, these models offer little or no incentive for health professionals to offer remote care or to use mHealth digital tools. Traditional reimbursement schemes based on fee-per-service and number of assessments performed reward a reactive approach to healthcare. Sickness-based care clashes with the mHealth potential, as it drives the change from a volume/service-based to a quality/value-based healthcare system. [14, 82] A good example of this paradigm shift is the one of Denmark, where the reimbursement model is not based on the number of medical acts performed but on the number of patients assessed, with the Health Ministry paying a negotiated flat fee per patient. This could be seen as an incentive to overcome the health professionals' reluctance to apply mHealth in their daily practices. [82, 99]

In some EU Member States, mHealth solutions adoption may benefit from the involvement of private stakeholders in the reimbursement decision tree process. For instance, insurance companies are taking a bigger role in funding mHealth companies and in reimbursing their solutions. [82] Since April 2014, in Germany, ophthalmologists are allowed to prescribe a smartphone app - Caterna Vision Therapy - as a complementary technique in the treatment of children with functional amblyopia. For the first time, children are allowed to practice their weaker eye in a playful way via a mobile app and the ophthalmologist can track progress of the treatment online because each exercise session is recorded automatically. This app is reimbursed by a statutory health insurance fund (Barmer-GEK). Other health insurers, like Axa, have followed their steps and also cover Caterna's treatment cost in Germany. Clinical studies have shown that Caterna Vision Therapy contributes to the success of eye patch therapy and increases the visual function of affected children. Moreover, besides being under specialist guidance and supervision, the Caterna Vision Therapy program is a certified medical device and carries a CE mark as affirmation of conformity with the essential requirements of the MDD. [100] This another positive example may pave the way for more reimbursement of mHealth solutions.

Reimbursement and funding systems can also provide financial incentives for fostering innovation in mHealth services. As an example, several German insurers reward healthy behaviors (such as getting health checkups, being a certain weight or actively using a fitness club) through small bonuses with values ranging from about €30 to €100, as well as reimbursement of fees for smoking-cessation or weight-loss courses. [28] This reimbursement fees approach could be used by insurers to foster the use of mHealth, particularly mobile medical apps. Indeed, mHealth solutions that can be classified as medical interventions and thus as integral elements of healthcare delivery should be subject to the same reimbursement conditions as other medical interventions.

6. CONCLUSION

European healthcare systems are struggling with financial sustainability problems arising from an ageing population and chronic diseases prevalence growth. Massive technological developments and increasing patient's empowerment and expectations became strong drivers for innovative and adaptive solutions. mHealth has the potential to drive the health sector towards a more efficient and decentralized healthcare as well as stimulate economic sustainability. Given all these possibilities and the prodigious advance in mobile technology, it is somehow surprising that the adoption curve of mHealth interventions keeps flatten. In fact, although the promising benefits are known and welcomed by the different players in the healthcare system, mHealth deployment in the EU has been slow and limited to small pilots. Regulatory uncertainty, data protection issues and lack of appropriate reimbursement models are appointed as main barriers to a wide adoption of this kind of technologies to deliver healthcare. Combined with a lack of interoperability standards among mHealth systems and the scarce evidence base to support mHealth's clinical and economic benefits, these pitfalls became serious roadblocks which can limit the adoption of mHealth.

While the risks associated with the use of mHealth applications should be clearly addressed, the focus of EU policy makers should be on fostering its opportunities. Taking into account that markets in the digital ecosystem are dynamic and complex, regulation must achieve its objective – a high degree of protection of the human life - in the most efficient and flexible way focused on an assessment of the market's performance against a set of objectives, which should evolve in parallel with technological improvements.

mHealth solutions, particularly mobile apps with an intended medical purpose, are subject to the provisions of the medical device regulatory framework. Several aspects of the current legislation were demonstrated to not be suitable for regulating this kind of tools.

In one hand, mHealth demands a single digital market and therefore the only appropriate approach to release its potential is at European level; this is hindered by the EU's own rules stating that health policy is a national competence and the EU can only complement the Member States' initiatives. On the other hand, the ambiguity of the law in regulating mHealth devices is a significant problem because State laws in Europe filter down from European Directives and must therefore be interpreted into national legislations.

Despite the Medical Devices Directive 2007 revision specifically included software in the definition of a medical device, uncertainty remains around the qualification of borderline lifestyle and wellbeing apps used for health-related purposes as well as the interpretation of "intended purpose" and "accessory" within the context of mobile medical apps. Since the current regulatory framework was built for medical devices with a very different development cycle from software, the unique characteristics of the software lifecycle - updates, beta testing and modularization - challenge an appropriate application of the EU regulatory process.

In an increasingly global and interdependent market, the adoption of consensual international standards to ensure that products are fit for their purpose are key to ensure economies of scale and boost innovation. The adoption of software development and lifecycle management standards, at the early stages of conception and product realization, can have a great impact on a developer's ability to create innovative products while ensuring user's safety. The recast of the current regulatory framework in the Medical Device Regulation to be effective in 2020 offers an important opportunity to clarify and harmonize these issues. While regulation of medical devices is necessary to ensure safety, the inevitable increase in consumer access to mHealth requires a more defined, targeted, and streamlined regulatory scheme for mobile devices in order to keep pace with this quickly evolving technology.

Although concerns are often raised about the processing of health data in the mHealth context, the current data protection framework, reformed and harmonized by the General Data Protection Regulation to be effective in 2018, provide a comprehensive and coherent set of rules to protect citizens' personal data across all technology platforms, including mobile devices, making specific provisions for special categories of data such as health data. By introducing new requirements – pseudonymization, Private Impact Assessments, appointment of Data Protection Officer - and making more stringent the existing ones – user's consent, breach notification - the General Data Protection Regulation requires companies handling EU citizens' data to undertake major operational reforms of processes and procedures to safeguard user's right to data protection. The guiding principles of "data minimization", "purpose limitation", "data protection by design" and "data protection by default" should be integrated in the full lifecycle of the app's development ensuring that data protection is carefully considered in the design and realization of these products.
Taking risk as the fundamental criterion in determining how the right to the protection of personal data may be safeguarded, European and national institutions should adopt a soft law approach by promoting codes of conduct and guidelines addressing privacy of data related to mHealth. The current initiative taken by the European Commission for an industry-led code of conduct on privacy and security for mHealth applications is a good example of this approach. Bearing the users rights in mind, companies dealing with personal data must now prepare to face the changes and additional requirements brought by the General Data Protection Directive. Regulators will need to exercise particular care in interpreting GDPR requirements to avoid stifling innovation and competitiveness in the digital and mobile sectors.

Interoperability between mHealth products will enable different systems to work together through the collection, storage and exchange of data in common formats, even boosting the possibility of plug-on-plug mHealth solutions. mHealth applications with their own proprietary data format, management and analysis impede data-sharing between systems, hampering one of the mHealth's benefit - greater access and availability of data. Facing a lack of interoperability standards, regulators must ensure that open standards and guidelines are established for device vendors, content developers and healthcare providers. The confidence and trust of both physicians and patients is expected to increase as well-defined and consistent ways to interact with mHealth solutions become widespread available.

The lack of evidence on clinical and economic benefits is one of the main roadblocks preventing a wider adoption of mHealth by providers, healthcare professionals and end-users. Rigorous clinical and cost-effectiveness studies are necessary to demonstrate the impact of mHealth interventions as well as the value of investing in mHealth innovations. Classical scientific practices, like randomized clinical trials, present a number of challenges and may not be suitable to generate clinical evidence for mHealth. In a fast-moving and innovative field, special attention should be given to the new and complex nature of these interventions when designing clinical studies.

Several studies demonstrated that health-related mobile apps lack high-quality and scientifically reliable content. Lack of oversight and content verification is hindering the selection of reliable mobile apps from those that are inaccurate or even fraudulent. This uncertainty on the reliability and accuracy of mobile app's content is a key barrier to their widespread adoption. Content certification led by healthcare professionals with specific expertise may be a useful approach to ensure a high level of safety.

As a complex intervention, the widespread adoption of mHealth will entail changes to the behavior of healthcare professionals and patients, and potentially require adaptation of infrastructures, systems or processes involved in healthcare delivery. The European Commission, through the 2020 Horizon Program, is making efforts to deploy high-speed and high-quality networks across the EU and support digital health literacy of healthcare professionals and citizens.

Many outstanding questions exist regarding reimbursement for mHealth apps and connected devices, such as who pays for what and under which conditions. In order to facilitate widespread access to mHealth, innovative and sustainable funding and reimbursement schemes that reward health outcomes and efficiency improvements need to be developed and implemented. Exchange of examples and good practices in this area needs to be promoted and facilitated at EU level. More studies substantiating improved health outcomes and cost-savings through the proliferation of mHealth are needed to encourage institutional stakeholders and payers to accelerate efforts for reimbursement. The creation of incentives to encourage both patients and healthcare providers to adopt mHealth, along with raising their knowledge and awareness about mHealth can also play a big role in its integration into the current healthcare delivery.

An ongoing and constructive dialogue between relevant stakeholders – developers/manufacturers, European and national Competent Authorities, healthcare professionals and end-users – is vital to ensure that safe and effective mobile health solutions for patients, healthcare professionals and healthcare systems are fully exploited. In this context, the current efforts of the European Commission seem to focus on creating an innovation-enabling environment across the EU through public consultations, revision of the medical device's legislation, development of codes of conduct and guidelines, promotion of frameworks and standards for interoperability, and further development of the data protection framework. Surely this will further contribute to the widespread adoption of mHealth in the European Union.

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