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Ensuring Evidence-Based Safe and Effective mHealth Applications

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Abstract. The Internet and the digitalization of information have brought big changes in healthcare, but the arrival of smartphones and tablets represent a true revolution and a new paradigm is opened which completely changes our lives. In order to validate the impact of these new technologies in health care, it is essential to have enough clinical studies that validate their impact in wellbeing and healthcare of the patient. Traditional regulatory organisations are still looking for their role in this area. If they follow the classical path of medical devices, we get to a technical, administration and economic collapse. This contribution first presents the main indicators showing the potential of mHealth adoption. It then proposes a classification of mobile health care apps, and presents frameworks for mHealth evaluation. Regulation of mHealth as part of the evaluation process is discussed. Finally, the necessary steps and challenges that have to be taken into account by the industry to prepare the entrance of these technologies into the EU market is analysed.

Keywords. mHealth, regulation, clinical evidence, framework, evaluation, smartphones.

1. mHealth as a transformative factor of care delivery in healthcare systems

Healthcare is based in a wide sense both on data and information. Up until recently it is hospitals and healthcare providers who have obtained and held this information, which has not been accessible to the people to whom it relates. Information to the citizen and patient on how to lead a healthy life has come from professionals, or in general advice texts. However, a transformation is now occurring whereby citizens can create and interpret large volumes of data to enable them to ensure a healthy lifestyle, as well as to interact with healthcare providers.

With the advent of Internet, called by Manuel Castell "*the information society"* [1], a new paradigm is opened which changes the way we live, work, communicate and enjoy our free time. The Internet and the digitalization of information have brought big changes, but the arrival of smartphones and tablets represents a true revolution. Everyone can be connected no matter where he/she is located. Information follows the person. Nowadays, most of the citizens in the world have a tool which has more capacity of data processing that those computers from decades ago that took up a whole floor of a building and cost dozens of millions of dollars. And above all, most of the

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population has an emotional connection to their smartphones. We only have to see how much we stress out when we forget our phone at home or when the battery goes dead and we have no chance to plug it in order to recharge it.

The number of mobile connections and subscribers to phone services is growing exponentially. By 2020, there will be 6.100 million people using smartphones, while nowadays (2015) there are 2.600 million [2][3]. The number of smartphone users is growing and also the number of healthcare applications.

In order to look at the evidence for safe mHealth applications, it is necessary to define what we understand by "Mobile Health" (mHealth). Below there are three different definitions of how mHealth is perceived from different perspectives:

- "*mHealth seeks to improve individuals' health and wellbeing by continuously monitoring their status, rapidly diagnosing medical conditions, recognizing behaviours, and delivering just in time interventions, all in the user's natural environment"* [4].
- *"Medical and public health practices supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices"* [5].
- *"mHealth also includes lifestyle & wellbeing applications, personal guidance systems, health information and medication reminders and telemedicine provided wirelessly"* [21].

mHealth covers different aspects of health, wellness, prevention, education, diagnostic, monitoring (with the use of wearables), follow up (treatment adherence) and contributes a new dimension to the collection of large amounts of data. Therefore we are not talking about using new technologies in healthcare, but how mobile technologies can help in the process of healthcare delivery transformation, covering various illnesses such as diabetes, heart failure, COPD, hypertension and mental health. But above all mHealth can open the door to personalized medicine, empowering the patient/citizen by providing bigger responsibility in the management of their health or condition.

One of the weak points of mHealth is the lack of sufficient number of empirical studies that validate their impact on wellbeing and health of the patient. Too frequently, studies on mHealth solutions have been based on "How can these technologies be introduced in the healthcare system?" instead of "How the healthcare systems can be more sustainable, more secure and efficient with the help of mHealth technologies?"

Lack of wide-spread agreement among experts on common research methods for mHealth assessment hinders the generation of reliable and comparable knowledge regarding the impact of mobile innovations. Also, many evaluations performed are based on specific disease groups, which limits their generalisability. Some evaluation studies provide neutral or negative results on the impact of eHealth; however, often, evaluations were conducted on pilots without having implemented the necessary organisational changes. Other evaluation studies point to positive impact of mHealth [5].

mHealth applications have grown exponentially. There are above 100.000 healthcare applications in the market including wearables, monitoring devices and others, getting to a "tsunami" of technologies that day by day invade the market. On the other hand, traditional regulatory organisations or medical evaluation institutions are still looking for their role in this area. If they follow the classical regulatory path of medical devices for mHealth, we may get to a technical, administration and economic

collapse, as the duration of the clinical trials enforced by regulation and the high costs associated make classical procedures unfeasible. Even more, mHealth solutions need regular updates which should also follow long and costly regulatory procedures. The FDA (Food and Drug Association, U.S.) has shown a cautious position by stating that there are "no binding recommendations" for mHealth regulation [13]. The European Commission has been also cautious and has initiated the mHealth Green Paper 2014, which consists of an open consultation without any recommendation as a result [21].

The lack of clear rules or guidelines for mHealth regulation is producing uncertainty in the industry and also lack of confidence of healthcare professionals. We need therefore to look for creative and innovative ways to create mHealth evaluation. At Mobile World Capital, we are working on this direction, searching consensus on a common framework for mHealth assessment among the different countries and European regions, through Medical Evaluation Agencies or similar organizations around Europe.

2. Socioeconomic impact and market readiness of mHealth

It is claimed in a report by PWC from June 2013 about the socio-economic impact of mHealth [14], "mHealth could save 99 billion EUR in healthcare costs in the European Union (EU) and add 93 billion EUR to the EU GDP in 2017 if its adoption is encouraged" (Figure 1). We might agree or not in this figure, but when thinking about these numbers, there is no doubt that it is worth giving mHealth a fair opportunity to realise and validate its potential.

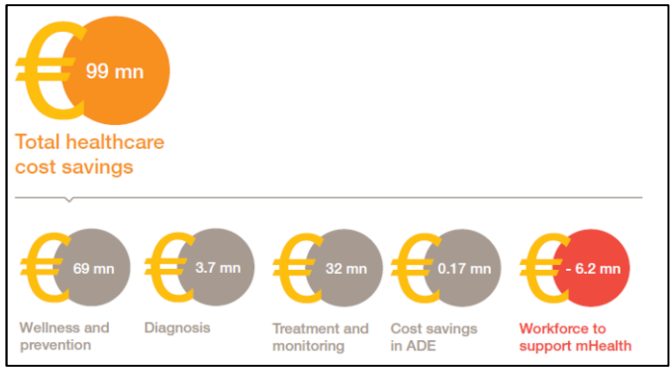

Figure 1. Economic impact of mHealth **Fehler! Verweisquelle konnte nicht gefunden werden.**

Aging population and chronic diseases are a major problem throughout not only Europe, but also around the globe [16]. As people become more aware of their condition and become more informed on their diseases through the technologies that provide availability to medical information, they can and should also start taking a much more active role in the management of their disease. Also, more and more people start focussing on wellness and prevention, which leads to good healthy habits, helps to avoid certain practices that are well known as triggers of certain future diseases, and provides citizens with tools, services and products that can help them to take an active role in the healthcare ecosystem. Many mHealth applications have this as their objective, but raise significant challenges in assessing their impact. This is also

congruent with the challenge of recognising that healthcare resources are limited both in terms of healthcare professionals and budget, and it is important that new models are brought into the system to face this new era we are entering into.

If we take a look at the benchmarking analysis carried out by Research2guidance on the mHealth App Market Ranking [17], "*Denmark, Finland, The Netherlands, Sweden and the UK offer the best market conditions for mHealth companies in the EU*". The main indicators that show a higher potential for mHealth adoption are:

- Regulatory frameworks for mHealth are in place, and guidelines on standards and interoperability following the European paths are adopted by trusted governmental bodies.
- High adoption of mHealth by healthcare professionals and patients/citizens, which lead to new service delivery processes and new communication channels to allow a much more active role of the patient.
- High level of digitalisation, integration and sharing of healthcare information by tools such as the electronic healthcare record, personal health record, ePrescription and many others.
- Strategic roadmap on mHealth is supported by the national government and policy makers that will facilitate the integration within the system at large scale.

In order to start with the deployment of mHealth within the EU, the industry should carefully choose those countries in which they will start the integration and penetration of this technology. As shown in the Figure 2 below, five countries offer the best market conditions for mHealth industry to establish new businesses [17].

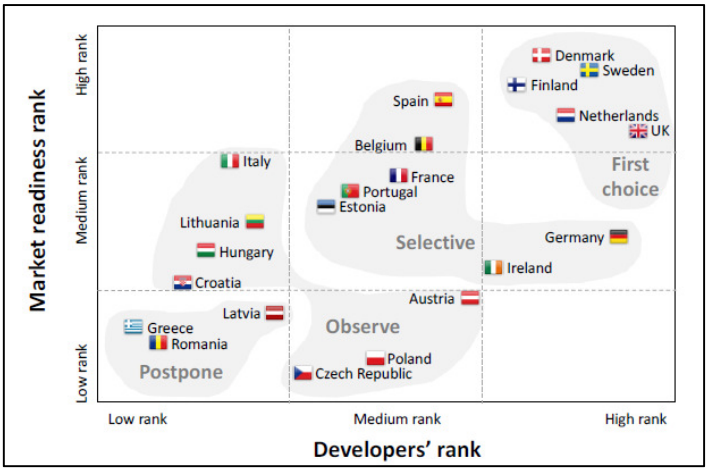

Figure 2. Country rank in market readiness for mHealth [17].

As indicated in the report on benchmarking analysis [17], "50% of the mHealth practitioners say that a good country ranking depends on how open doctors are for applying and integrating mHealth solutions into their patient treatments and communication. As there is no general reimbursement of mHealth services in all EU countries, this high rating of the doctor channel in the top country builds more on their

general openness to use new technologies rather than the existence of business models for doctors and mHealth services that work already today".

One important set of players for acceptance and deployment of mHealth services is the governments and policy makers. Once they become aware of the benefits and potential of mHealth, they have to play also a very active and important role in spreading those benefits among the citizens and making possible the integration within the healthcare system. The establishment of concrete roadmaps and action plans aligned with the political agendas will help to position the country as a leading player for mHealth deployment in the EU scene.

3. Classification of mobile 'apps' and related solutions in healthcare

Although the number of mobile health apps is large and growing, most have only simple functionalities built into them. An analysis [18] of the apps available to consumers through the iTunes app store resulted in categorization of apps based on whether they could:

- **Inform**: Provide information in a variety of formats (text, photo, video)
- **Instruct**: Provide instructions to the user
- **Record**: Capture user entered data
- **Display**: Graphically display user entered data/output user entered data
- **Guide**: Provide guidance based on user entered information, and may further offer a diagnosis, or recommend a consultation with a physician/a course of treatment
- **Remind/Alert**: Provide reminders to the user
- **Communicate:** Provide communication with HCP/patients and/or provide links to social networks

There is a small subset of apps with complex functionality (e.g. electrocardiogram (ECG) readers, blood pressure monitors, blood glucose monitors), however it is recognized that most of the mHealth apps available today are only simple in design and do little more than provide information.

An alternative approach to classify mobile applications is to place them according to their use as part of the care continuum, sometimes called the "patient journey": overall wellness and healthy living, diagnosis/self-diagnosis, healthcare professional visit, follow up and further information, prescription filling and medication compliance [18].

The working group on mHealth assessment of the Agency for Health care Quality and Assessment of Catalonia (AQuAS) and the mHealth Competence Centre of Mobile World Capital has developed and suggests a new taxonomy for classification of mHealth applications and services which combines the three aspects: 1) functionality and intended use, 2) type of clinical condition, and 3) potential risk (Figure 3).

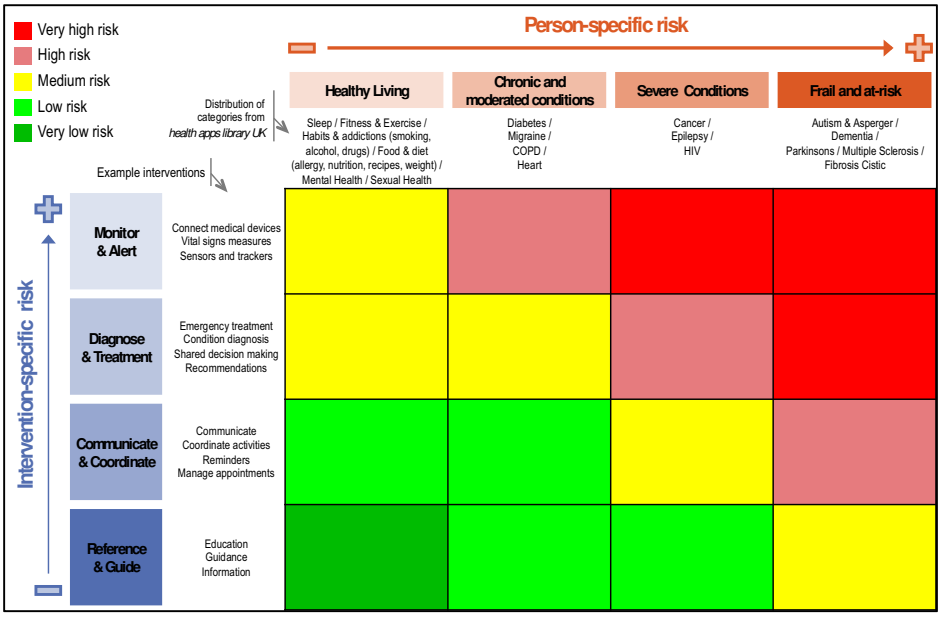

Figure 3. Proposed taxonomy of mHealth and related risks on the use of the solution for patient safety by AQuAS and MWC©.

4. Frameworks for mHealth evaluation

In order to inform policy and user decisions, generation of reliable scientific evidence of mHealth benefits through systematic evaluation is crucial. There is need to assess the impact and empirically demonstrate benefit and best use of mHealth solutions as part of care delivery and health/disease management. However, health care innovations based on mHealth solutions have several features that make scientific evaluation challenging, such as fast technologic turnover and strong influence of design and organizational context. To answer the particularities of mHealth applications and services, the evaluation approach should be iterative and involve the views of all relevant stakeholders early in the process. Some initiatives exist for rating, validation and certification of marketed mobile apps, but these offer partial assessment generally focused on usability and data privacy and protection (such as myhealthapps.net, AppSaludable, HealthApp Library NHS, iMedical apps) [30].

On the other hand, there are numerous frameworks and models developed for evaluation of eHealth services (including health IT and telemedicine) and these are extensively based on commonly accepted evaluation methodologies, such as Health Technology Assessment. After a review and analysis of these, they could be easily adapted to meet mHealth evaluation needs through an overarching assessment approach (Table 1).

Table 1. Key evaluation frameworks for telemedicine and health IT that could be adapted to mHealth evaluation.

	Telemedicine	Health IT systems	
Reference	**Kidholm K et al. 2012 [27]** A model for assessment of telemedicine applications: MAST.	**Catwell & Sheikh, 2009 [28]** Evaluating eHealth interventions: the need for continuous systemic evaluation	**Yusof et al. 2008 [29]** An evaluation framework for health information systems: human, organization and technology-fit factors (HOT-fit)
Target group	Health professionals, patients, managers, policy makers.	Developers/design teams	Researchers, practitioners s (clinicians/GPs)
Goal/ Approach	Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. It is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related	Comprehensive overall evaluation approach, multifaceted, multidisciplinary approach and facilitates continuous systematic evaluations throughout the lifecycle of an eHealth intervention.	Provides evaluation dimensions for addressing the fit between human, organization, and technology factors. HOT-fit should be applied in a flexible way, taking into account different contexts and visions, stakeholders' point of views, phases in the system development life cycle, and evaluation methods.
Foundation	Literature review, EUNetHTA, IOM	Literature: 1) cognitive and usability engineering methods for the evaluation of clinical information systems, 2) socio-technical and contextual considerations	1) The IS Success Model of DeLone & McLean, 2) The IT-Organization Fit Model,3) Literature review; critical appraisal of health information systems studies; 4) Pilot testing developed framework (case study clinical setting)
Dimensions	***Preceding considerations*** Purpose of the telemedicine application? Relevant alternatives? International, national, regional or local level of assessment? Maturity of the application? ***Multidisciplinary assessment*** 1) Health problem and characteristics of the application 2) Safety 3) Clinical effectiveness 4)Patient perspectives 5) Economic aspects 6) Organizational aspects 7) Socio-cultural, ethical and legal aspects Transferability assessment: 1) Cross-border, 2) Scalability, 3) Generalizability	Documenting the complex relationships between: (1) political, (2) social, (3) organizational, and (4) technical worlds. Continuous systematic evaluations (eHealth intervention lifecycle: (1) inception (e.g. vision, goals & needs) (2) requirements & analyses (3) design, develop & test (4) implement & deploy	1) Human factors: system use, user satisfaction 2) Technology factors: system, information, and service quality 3) Organizational factors: structure, environment, communication, 4) Net benefits: impact on users, performance; efficiency, effectiveness, etc.; organizational impact (e.g. costs); clinical impact (quality of life, care, communication/ information access).
Evaluation methods	Measure efficacy, effectiveness, safety, usual methods are: RCT, cohort studies, quasi-experimental design Economic evaluation; cost-	1) Formative iterative evaluations using simple prototypes of the eHealth intervention may be used for requirements	Qualitative, quantitative or a combination of both approaches: 1) Formative evaluation to identify system problems

	effectiveness analysis Qualitative approach: interview, focus group, questionnaires, etc.	elicitation and analyses 2) Once a working model of the system is available, empirical evaluations can be completed, which could include the collection of quantitative and/or qualitative data, depending on the goals and scope of the study and the stage of development	as they emerged and to improve the system as it was developed, 2) Qualitative methods to generate a fuller description of the healthcare setting and its cultural issues and to understand why the system functioned well or poorly in a particular setting. Face-to-face interviews (including users, clinicians and IT staff) about their system us

5. Regulation of mHealth as part of the evaluation process

Despite the fact that mHealth applications are numerous and getting more popular due to all the potential benefits described above, they are still under regulated and may pose risks to the health and safety of consumers, as well as to the privacy and security of consumer health information.

Health and safety refers to the physical health and wellbeing of a user of the application. Characteristics of the application that have influence on patient safety are related to its functionalities - in particular to the appropriateness, accuracy and reliability of used information. For example, a mHealth application may provide inaccurate information or recommendations on how to treat a condition causing negative impact on a patient's overall health.

On the other hand, patient privacy and security refers to safeguarding protected health information (PHI) [18]. Privacy is an individual's right to control access to his/her PHI. Security is the device's or user's ability to protect PHI from unauthorized disclosure either when stored on the device or transmitted to another device. Security requires technical safeguards, such as encryption, workstation security, and access controls, while privacy focuses more on an organization's policy and procedure for protecting PHI [20].

Safety and transparency of information were identified as one of the main issues for mHealth uptake in the public consultation on the Green Paper on mobile health of the European Commission [21]. In the public consultation, a majority of respondents thought that safety and performance requirements of lifestyle and wellbeing apps are not adequately covered by the current EU legal framework while calling for a strengthened enforcement of data protection and medical devices rules.

For conventional medical devices, all these issues are addressed by the manufacturer who must fulfil the requirements establish by the relevant regulatory authorities. Patient safety is thus guaranteed by controlling that only safe and effective devices reach the market.

Currently, the debate around the regulation of mHealth applications and services is getting momentum and classification algorithms are proposed by FDA and the European institutions to support decisions as to whether a certain mHealth application is a medical device or not. A governing principle in both regulations is the concept of "intended use" of the application and this determines the applicability of medical device regulation. Updates and amendments of existing regulation are currently

underway in both the US and the EU in order to better respond the needs for evaluation and marketing of mobile applications for health use [22].

In February 2015 the US Department of Health and Human services at the FDA issued Guidance for Industry and FDA staff on Mobile Medical Applications to explain the position of FDA on this topic [22]. In order not to stifle innovation and waste resources, FDA decided to limit its regulatory reach by identifying clearly the specific group of mobile applications which are subject of regulation. Thus, three categories of mobile apps are defined:

a) Regulated mobile medical apps (those complying with the definition of medical device)
b) Mobile apps subject to enforcement discretion (may meet the definition of medical device, but pose a lower risk to the public)
c) Unregulated mobile apps (do not meet the definition of medical device)

The majority of available mobile apps on the market currently fall in the unregulated groups b) and c). There are six subcategories within the category b) enforcement discretion and each of them has a policy basis for existing [23]:

1. Patient self-management
2. Patient trackers
3. Access to contextually relevant information
4. Patient communication and telemedicine
5. Simple, professional calculators
6. Connectors to Electronic Health Records

In this guidance, the FDA lists a number of examples of mobile apps, to assist manufacturers in determining if a product is a mobile medical app and to follow the associated controls established by the regulation.

In the EU there is no integrated health regulation framework with a single regulatory body, such as the FDA in the US. The EU regulates mHealth in a number of ways: by means of medical devices regulation, regulation of personal health data, reimbursement of healthcare rules, and product liability. To be legally introduced in the EU market, a medical device should bear the Conformité Européenne (CE) mark. The CE mark states that the device has been assessed before being placed on the market and meets EU safety, health and environmental protection requirements. mHealth as a service is not regulated, but the software to provide the service is under the e-Commerce directive (SaaS: Software as a Service) [34].

The European medical device directive (MEDDEV2007/47) contemplates the software (stand-alone) in the definition of the medical device. Particularly, according to the EU directive, a medical device is defined as: “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, and 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 by

such means". Thus, since a mobile app is a software, it is a medical device if its intended use falls within the above definition.

An effort is needed to implement the medical device regulations to the mobile app market, since the market of the medical devices, with which the competent authorities for medical devices of the member states are familiar, is far different from that of the mobile apps [24].

We can conclude that existing regulations (FDA, CE mark) are relevant to address certain risks, but cover only mHealth technologies classified as medical devices. A broader evaluation of the impact of mHealth services should be coherent with existing regulation for medical devices but goes beyond it. In this sense, regulatory requirements can be considered as part of the initial stages of an evaluation approach. In order to inform policy and practice decisions, further generation of reliable scientific evidence through systematic evaluation is crucial to assess the impact and empirically demonstrate benefit and best use of mHealth solutions as part of care delivery and health and disease management.

6. Challenges for implementation and adoption of mHealth solutions

Multiple barriers, such as regulatory, economic, structural and technological, are limiting the adoption of mHealth. Also, the non-existence of clear business and exploitation models behind the implementation of mHealth services makes it difficult to expand and deploy these new technologies for the benefit of patients and professionals. The industry still is a little reluctant to invest efforts and budget in certain pilots and initiatives that seem to be far from the market.

The main two changes foreseen for 2020 in the field of mHealth are around *data integration* and *interoperability* of services and platforms [25]. Both are necessary to support sharing of information between patients and professionals, healthcare centres and easy implementation of new solutions. Both will help avoiding isolated silos that decentralise information and make difficult the taking of decisions based on an aggregated pull of data available. Also, in the next coming years, it is foreseen that more and more medical apps will be developed and introduced in the market as a regulatory and legal framework is being agreed and adopted in the EU.

When looking into the biggest barriers for deployment, privacy issues and clear regulation frameworks are the most relevant issues that have been identified. This is not a surprise, since data management and sharing in the field of healthcare is one of the most important topics and goes directly linked to the use of technologies.

In order to encourage the adoption of these new solutions, it is important to take into account some actions that can facilitate the process, as for example the approval of an mHealth strategic plan within the regional or national strategies of the healthcare and social government departments. Also, adding up to the regulatory framework, the creation of innovative business models to provide sustainability of both health services and information/IT services which at the same time fulfill the objectives of all stakeholders implied in the process is important. And last, it is important to raise awareness among citizens, patients and professionals, through training programs and communication campaigns that show the benefits and added value coming from mHealth.

Another concern raised by professionals in the field is the lack of clinical evidence linked to the impact of mHealth solutions. As seen in Figure 4, very little scientific

evidence yet exists. This, together with the weak regulatory situation makes it difficult for professionals to act as "prescribers of apps" for the patients.

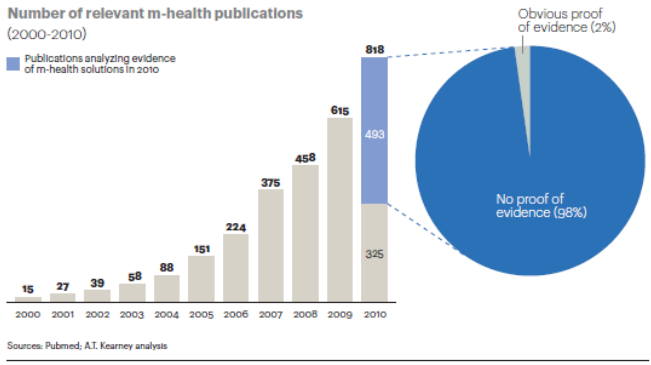

Figure 4. Number and level of evidence of mHealth publications 2000 - 2010 [26].

To overcome the barriers mentioned above (regulatory, economic, structural and technological), strong support from policy makers is needed which will enable and accelerate adoption by the system and final users. They need to "formulate policies that can drive adoption of mHealth solutions. The national and regional payers need to support these policies by creating facilitative reimbursement mechanisms that ease the adoption of mHealth solutions across patients and healthcare providers".

As a summary, for each barrier identified that prevents from deploying mHealth, some actions to be executed are proposed below:

Regulatory framework

Actions needed:

- Regulations should effectively address issues as certification, standardization and interoperability to help increase the confidence and trust of both healthcare professionals and patients.
- Concrete roadmap and timeline on when relevant policies and regulations may be introduced and what might be addressed by such measures should be developed.
- Regulations should be pro-innovation and aimed at introducing measures that enable affordable and ubiquitous healthcare.

Standardization and Interoperability

Actions needed:

- Regulators have to work together to ensure interoperability and standardization guidelines for various mobile health ecosystem participants (device vendors, content creators and healthcare providers).
- Ensuring standardization and interoperability among solutions will help
    - plug-and-play solutions development
    - easy adoption for end-users
    - facilitate scaling

Certification of Applications

Actions needed:

- Regulators should facilitate speedy approvals for vendors and software developers.
- The intent of governments and regulators should be to enable the rapid creation of a healthy mobile health ecosystem that benefits both patients and market players.
- It is important for regulators to follow a harmonized approach to ensure greater applicability of certified devices and applications across regions to encourage greater participation of device vendors and solution developers.

Recommended further readings

1. GSMA and PA Consulting, *Policy and Regulation for Innovation in Mobile Health.* Report 2011. http://www.gsma.com/mobilefordevelopment/wp-content/uploads/2012/04/policyandregulationforinnovationinmobilehealth.pdf, last access 11 February 2016.
2. Cusack CM et al., *Health information technology evaluation toolkit: 2009 Update,* AHRQ publication No09-0083-EF, Agency for Healthcare Research and Quality, Rockville, MD.
3. Nykänen P et al., Guideline for good evaluation practice in health informatics (GEP-HI), *Int J Med Inform* **80** (2011), 815–27.
4. Kumar S et al., Mobile health technology evaluation: the mHealth evidence workshop, *Am J Prev Med* **45**(2) (2013), 228-36.
5. Rigby M et al., Evidence Based Health Informatics: 10 Years of Efforts to Promote the Principle, in: Sérousi B, Jaulent M-C, Lehmann CU (eds.), *Evidence-based Health Informatics – IMIA Yearbook of Medical Informatics,* Schattauer, Stuttgart, 2013. pp 34-46.

Food for thought

1. Which clinical areas can benefit the most from mHealth solutions?
2. Which kind of role can have patients/citizens/consumers on the regulatory and legal process, and is this appropriate?
3. Why is the US mHealth market growing faster than the EU market?
4. What do you think about the taxonomy proposed by AQuAS and MWC (compare Figure 3)?

References

[1] M. Castells, *The Rise of the Network Society,* in: The Information Age: Economy, Society and Culture. 2nd ed., Wiley Blackwell, Oxford, 2010.
[2] *GSMA intelligence*, https://gsmaintelligence.com, last access 11 February 2016.
[3] *Ericsson Mobility report*, http://www.ericsson.com/ericsson-mobility-report, last access 11 February 2016.
[4] S. Kumar, W. Nilsen, M. Pavel, M. Srivastava, Mobile health: Revolutionizing healthcare through transdisciplinary research, *Computer* **46**(2013), 28-35.

[5] WHO, *mHealth – New horizons for health through mobile technologies*, Global Observatory for eHealth, vol 3, http://www.who.int/goe/publications/goe_mhealth_web.pdf, last access 11 February 2016.
[6] R.S. Valdez, R.J. Holden, L.L. Novak, T.C. Veinot, Transforming consumer health informatics through a patient work framework: connecting patients to context, *Journal of the American Medical Informatics Association* **22**(2015), 2-10.
[7] M. Fiordelli, N. Diviani, P.J. Schulz, Mapping mHealth research: A decade of evolution, *Journal of Medical Internet Research* **15**(2013): e95.
[8] C. Free, G. Phillips, L. Galli, L. Watson, L. Felix, P. Edwards, V. Patel et al, The Effectiveness of Mobile-Health Technology-Based Health Behaviour Change or Disease Management Interventions for Health Care Consumers: A Systematic Review, *PLoS Medicine* **10**(2013).
[9] N.G. Cortez, I.G. Cohen, A.S. Kesselheim, FDA Regulation of Mobile Health Technologies, *New English Journal of Medicine* **371** (2014), 372-379.
[10] S.R. Steinhubl, E.D. Muse, E.J. Topol, Can mobile health technologies transform health care? *JAMA* **310**(2013), 2395-6.
[11] P. Klasnja, W. Pratt, Managing health with mobile technology, *Interactions* **21** (2014), 66-69.
[12] P.R. Sama, Z.J. Eapen, K.P. Weinfurt, B.R. Shah, K. Schulman, An Evaluation of Mobile Health Application Tools, *JMIR mHealth and uHealth* **2**(2014), e19.
[13] R.S. Weinstein, A.M. Lopez, B.A. Joseph, K.A. Erps, M. Holcomb, G.P. Barker, E.A. Krupinski, Telemedicine, telehealth, and mobile health applications that work: opportunities and barriers, *American Journal of Medicine* **127**(2014):183-7.
[14] US Food and Drug Administration, *Guidance for Industry and Food and Drug Administration Staff: Mobile Medical Applications,* Document issued on 9 of February 2015, http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf, last access 11 February 2016.
[15] PricewaterhouseCoopers, *Socio-economic impact of mHealth: An assessment report for the European Union*, June 2013, http://www.gsma.com/connectedliving/wp-content/uploads/2013/06/ Socio-economic_impact-of-mHealth_EU_14062013V2.pdf, last access 11 February 2016.
[16] OECD, *Health at a glance: Europe 2012*, 2012, http://ec.europa.eu/health/reports/european/health_glance_2012_en.htm, last access 11 February 2016.
[17] Research2Guidance, *EU Countries' mHealth App Market Ranking*, 11th may 2015.
[18] IMS Institute, *Patient Apps for Improved Healthcare. From novelty to mainstream*, October 2013
[19] HIPAA, '*Protected Health Information': What Does PHI Include?* http://www.hipaa.com/hipaa-protected-health-information-what-does-phi-include, last access 11 February 2016.
[20] D.F. Schulke, The regulatory arms race: mobile-health applications and agency posturing, *Boston University Law Review* **93** (2014), 1699-1752.
[21] European Commission, *Green paper on mobile Health (mHealth)*, Brussels, April 10, 2014, http://ec.europa.eu/newsroom/dae/document.cfm?doc_id=5147, last access 11 February 2016.
[22] FDA, *Mobile medical applications*: *Guidance for Industry and food and drug Administration Staff.* February 9, 2015, http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf, last access 11 February 2016.
[23] B.M. Thompson. *FDA Regulation of Mobile Health* (2nd ed). Chester Street Publishing, USA, 2013.
[24] F. Censi, E. Mattei, M. Triventi, G. Calcagnini, Regulatory frameworks for mobile medical applications, *Expert Review Medical Devices* **12**(3) (2015) 1-6.
[25] Research2Guidance, *mHealth App Developer Economics report*, May 2014.
[26] ATKearney, *Improving the evidence for mobile health*, 2011.
[27] K. Kidholm, A.G. Ekeland, L.K. Jensen, J. Rasmussen J, C.D. Pedersen, A. Bowes, S.A. Flottorp, M. Bech, A model for assessment of telemedicine applications: MAST, *International Journal of Technology Assessment in Health Care* **28**(2012), 44-51.
[28] L. Catwell, A. Sheikh, Evaluating eHealth interventions: the need for continuous systemic evaluation, *PLoS Medecine* **6**(2009), e1000126.
[29] M.M Yusof, J. Kuljis, A. Papazafeiropoulou, L.K. Stergioulas, An evaluation framework for Health Information Systems: human, organization and technology-fit factors (HOT-fit), *International Journal of Medical Informatics* **77**(2008), 386-98.
[30] *My health apps,* http://myhealthapps.net, last access 11 February 2016.
[31] *Estrategia de calidad y seguridad en aplicaciones móviles de salud,* http://www.calidadappsalud.com, last access 11 February 2016.
[32] *Health apps library*, http://apps.nhs.uk, last access 11 February 2016.
[33] *iMedicalApps*, http://www.imedicalapps.com, last access 11 February 2016.

[34] European Commission, *Guidelines on the qualification and classification of stand-alone software used in healthcare within the regulatory framework of medical devices*, http://ec.europa.eu/health/medical-devices/files/meddev/2_1_6_ol_en.pdf, last access 11 February 2016.