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Trusting telemedicine: A discussion on risks, safety, legal implications and liability of involved stakeholders

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ABSTRACT

Objectives: The main purpose of the article is to raise awareness among all the involved stakeholders about the risks and legal implications connected to the development and use of modern telemedicine systems. Particular focus is given to the class of "active" telemedicine systems, that imply a real-world, non-mediated, interaction with the final user. A secondary objective is to give an overview of the European legal framework that applies to these systems, in the effort to avoid defensive medicine practices and fears, which might be a barrier to their broader adoption.

Methods: We leverage on the experience gained during two international telemedicine projects, namely MobiGuide (pilot studies conducted in Spain and Italy) and AP@home (clinical trials enrolled patients in Italy, France, the Netherlands, United Kingdom, Austria and Germany), whose development our group has significantly contributed to in the last 4 years, to create a map of the potential criticalities of active telemedicine systems and comment upon the legal framework that applies to them. Two workshops have been organized in December 2015 and March 2016 where the topic has been discussed in round tables with system developers, researchers, physicians, nurses, legal experts, healthcare economists and administrators.

Results: We identified 8 features that generate relevant risks from our example use cases. These features generalize to a broad set of telemedicine applications, and suggest insights on possible risk mitigation strategies. We also discuss the relevant European legal framework that regulate this class of systems, providing pointers to specific norms and highlighting possible liability profiles for involved stakeholders.

Conclusions: Patients are more and more willing to adopt telemedicine systems to improve home care and day-by-day self-management. An essential step towards a broader adoption of these systems consists in increasing their compliance with existing regulations and better defining responsibilities for all the involved stakeholders.

1. Introduction

Over the years a number of different definitions of telemedicine have been proposed [1], but almost all of them share the key elements identified by the American Telemedicine Association: Telemedicine is the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status [2]. This broad definition focuses on the exchange of a specific type of information (health-related), on the means of communication used (electronic) and on the overall goal (improve health status) rather than being very specific about technical details. As a result, telemedicine applications are pretty diverse in terms of specific purposes and implementation. Norris [3] identified 4 main areas where a relevant number of telemedicine applications have focused. These consist in teleconsultation, tele-education, telesurgery and telemonitoring. However, in recent years, telemonitoring systems evolved beyond the simple remote monitoring functionalities empowering active, non-mediated, interactions with the patients. We will refer to these systems as "active" telemedicine systems in the following of the article. Some systems, after physicians have properly set them up, may suggest the patient to perform actions in response to certain events (e.g. take a certain medication if you're experiencing a specific symptom) while others push the automation further beyond and implement a closed loop control of a clinical variable to keep it in a safe range (e.g. blood glucose for

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diabetic patients, controlled using insulin). With the exception of telesurgery, which immediately raised ethical and legal concerns due to its strict connection to risky surgical procedures [4,5], this new generation of active telemedicine systems comprises the systems that more than others pose relevant challenges regarding liability and legal issues due to the risks associated with their development and use.

1.1. Background and related work

Discussion on the legal and ethical implications of remotely exercised medicine started even before specifically designed telemedicine systems were developed. The first applications that involved consultation of a doctor who was not physically present, even using the simplest forms of communication such as telephone or email, already raised concerns about the modification of the doctor-patient relationship [6] and legal jurisdiction to apply in the case of litigation [7]. In the last 10–15 years, telemedicine has become more pervasive and debate about its legal and security implications has arisen in the communities of several clinical domains including telepathology [8], teleradiology [9], chronic diseases management [10,11] and even in the less common application of telepsychiatry [12]. Recently, the growing development of mHealth significantly improved the diffusion of telemedicine. According to the mHealth definition, provided by the World Health Organization (http://www.who.int), mobile devices, such as smartphones, wearable devices or personal digital assistants, are the new way to support the medical and public health practice [13]. As a matter of fact, their rapid expansion definitely reduced technological barriers and costs for the development of telemedicine applications, where the central hub is more often going to be the Smartphone.

The sheer number of available medical or health-related apps have raised debates involving legal implications and security requirements [14,15], highlighting the low level of maturity of this area. The lack of a standard guideline or an official harmonized regulation for mobile apps development and deployment leaves to the developers the overall responsibility concerning safety and quality. Even though both users and developers are getting more aware of this issue, Martinez-Perez et al. [16] highlighted that the current regulations in USA and Europe are still not up to date with latest technology and thus difficult to follow.

A review article by Broens et al. [17] highlighted legislation and policy as one of the five main determinants for successful telemedicine adoption and a similar result was obtained in the analysis of the Information Technology Supplement to the American Hospital Association's 2012 annual survey [18]. As a further testimony to the criticality of the topic, in recent years, centers dedicated to the relationship between ethics, legislation, risk and telemedicine have been established both in Europe and USA [19,20]. Already in 2000 Stanberry [21] pointed out how telemedicine has the potential to create new clinical risks and responsibilities, highlighting the need for better education and guidance for medical professionals about the practical and professional issues that may arise. A risk assessment model for mHealth has been discussed by Lewis and colleagues in a recent paper [22]. The authors suggest classifying mobile medical apps depending on three main dimensions: probability and severity of the potential harm, complexity of the system, and presence of contextual factors that may cause further risks. The proposed model is however directed only to the risk assessment phase and does not provide insights on specific mitigation strategies or details about the relevant regulatory issues and legislation. On the other hand an interesting recent work by Garell et al. [23] proposed a legal framework, in the context of European legislation, to support designers in the development and assessment of digital health services. However, the study addressed the rather broad scope of digital health services at large, thus not focusing on telemedicine application and their peculiarities (e.g. the presence of a set of devices operated directly by patients, dependency from mobile connectivity, etc.). Moreover, the proposed framework is mostly directed to system developers, leaving other stakeholders' perspectives out of scope.

1.2. Motivation and objectives

Modern telemedicine systems involve a wide range of stakeholders, each caring about their own responsibility. Despite the most important role is often attributed to system designers and developers [23] also physicians can be held responsible for malpractice [24] connected to the use of telemedicine. Furthermore also other healthcare professionals like nurses have their responsibilities and workflows changed by the presence of telemedicine [25,26]. The central role of nurses becomes significant especially in telemedicine systems adopted in the homecare settings, where patients have to be introduced to the use of new technology and empowered to perform self-management. Moreover, nurses are often responsible for the daily patients control through the use of remote monitoring systems [27]. Also pharmacists are increasingly acquiring a front-line role in many public health initiatives involving uncomplicated conditions [28,29], with the possibility of being supported by teleconsultation when needed. Finally a frequently overlooked but ethically and legally crucial fact is that home telehealth turns patients (and their significant others) into active co-participants in the delivery of health care [30].

All those issues have been repeatedly tackled over time by the researchers at the Laboratory of Biomedical Informatics of the University of Pavia, which has a long standing record of designing and implementing telemedicine systems. The group started with the remote monitoring of diabetes patients operating through modems over land lines across the turn of the century [31], then moved to using the web [32] and finally switched to mobile applications [33] following the technology evolution. Other experiences have also addressed designing systems for educating patients and improving their compliance to treatments through reminders and notification [34] or even supporting the use of standard protocols by paramedics [35]. More recently, we have been involved in the design and implementation of two major projects, namely MobiGuide and AP@home, funded by the European Union within the 7th Framework Programme; both projects comprised a telemedicine component. We leverage on the problems and perspectives raised by these projects to create a map of the potential criticalities of active telemedicine systems, and provide some insights into the European legal framework that is relevant for them.

The purpose of this article is thus to raise awareness among all the involved stakeholders and avoid defensive medicine practices and fears that might be a barrier to broader adoption in clinical practice of these otherwise very promising systems. We decided to leave issues regarding privacy and confidentiality of health data out of the scope of the present article, which instead primarily focuses on medical liability and on potential risks of harming patients.

2. Methods

We organized two workshops in Pavia in December 2015 and March 2016 where the theme of the potential criticalities of active telemedicine systems has been discussed in a round table with system developers, researchers, physicians, nurses, legal experts, healthcare economists and administrators. As already mentioned, we leveraged on the two European projects MobiGuide and AP@home to trigger the discussion and identify the main features and associated risks of active telemedicine systems. In the following we briefly present an overview of the two systems, namely MobiGuide and AP@home while in the results section we present a detailed list of identified critical points along with some mitigation strategies. Finally, in discussion section we provide insights on the most relevant European regulations that constitute the legal framework for the development and safe usage of active telemedicine applications.

2.1. Mobiguide

The MobiGuide project (www.mobiguide-project.eu) developed a

mobile, distributed and personalized decision-support system (DSS) for patients with chronic illnesses and their care providers. The system has been designed to be disease-generic, and thus was able to address two different clinical domains: atrial fibrillation and gestational diabetes [36]. The system is based on computer-interpretable representations of clinical practice guidelines that allow executing the guideline knowledge with a patient's data to produce patient-specific recommendations. Part of these recommendations are directly delivered to patients [37] through their smartphone interfaces: reminders to take measurements (like blood pressure, ECG, blood glucose), reminders to take medications at specific times according to the prescription plan, or even clinical recommendations like diet modifications or appropriate actions to take when they are feeling a symptom. Another type of recommendations MobiGuide can generate is directed to physicians. These include suggesting to change/adjust pharmacological therapy, proposing therapeutic procedures for eligible patients (e.g. cardioversion for atrial fibrillation patients) and performing specific diagnostic tests/procedures. The DSS provides guidance to patients and physicians using clinical data coming from an integrated personal health record (PHR) [38], which collects data from the hospital EMR and patient-generated data thanks to the use of the Smartphone interface or using a set of Bluetooth connected sensors (depending on the domain these can consist for example in an ECG monitoring belt or a blood glucose and blood pressure meters). Supplementary Fig. 1 provides an overview of the system architecture.

Two observational pilot studies were performed on the two clinical domains: GDM patients used the MobiGuide application for an average of 2 months (and up to 3 months), and AF patients used it for an average of 4.2 months (and up to 9 months). The population was very different in the two studies: while in GDM the patients (20 cases) were Spanish women with an average age of 35 and experienced with technology, AF patients (10 cases) were older, chronic patients, with additional comorbidities and much less experienced with technology. The whole duration of the study was April-December 2015.

2.2. AP@Home: bringing the artificial pancreas at home

The main goal of the AP@home project [39] was to improve the treatment of adult patients affected by Type 1 Diabetes (T1D) administering their insulin therapy through the so called Artificial Pancreas (AP). The AP is a minimally invasive device for the automatic glycemic control in T1D, modulating insulin infusion in closed loop based on the real time measurements of blood glucose [40]. Thus an AP encompasses a sensor for continuously acquiring blood glucose readings, a pump that delivers the insulin boluses to the patient and a control algorithm driving the pump with the right amount of insulin to be administered each time. Even though the MiniMed 670G by Medtronic (Minneapolis, MN; USA) providing basic AP functionality has been certified for commercial use by the FDA in Fall 2016 (http://www.accessdata.fda.gov/cdrh_docs/pdf16/P160017a.pdf), the AP was just a medical investigational device exploited in clinical experiments across the whole AP@home timeframe (2010–2015). To simulate real-life conditions, those experiments had to assess its performance over a reasonable time frame, including the possibility of running unattended and being managed solely by the patient. Thus, during the 5 years of the project several observational studies were planned enrolling patients over longer times and accomplishing experiments in environments getting each time closer to real-life conditions. Those started in 2011 with patients undergoing a single day admission to hospital under strict protocol prescriptions [41]; increased to a 2 day hotel stay during the years 2012–2013 [42] and eventually ended in 2014–2015 with a major trial enrolling 30 adult patients for a period of 2 months [43] at their homes.

The main goal of AP@home addressed the implementation of the AP as a medical device and was mostly concerned with modeling and control methodologies for regulating insulin delivery. Nevertheless, telemedicine was seen from the beginning as an ancillary but essential component since the nature of the AP as an active medical device running unattended represented a safety hazard indeed. Thus a telemedicine component has been designed straight from the project inception [44], was implemented and tuned during the early experiments of the project accomplished in a safe controlled environment at the hospital [45] and then used throughout all the remaining experiments [46], resulting in the arrangement shown in Supplementary Fig. 2.

Moreover, the availability of that component was fundamental to obtain approvals for the studies by the Ethics Committees of the clinical institutions that were allowed to accomplish the unsupervised experiments, preserving patient safety throughout all of them. In fact, the remote monitoring service allowed to spot several problems mainly occurred during the early hotel studies, in particular overnight when the patient was asleep [47]. The notifications of that service always caused the prompt intervention of the staff that managed the problem.

On the wake of the successful completion of AP@home, an additional study was scheduled on children using the same hardware, on the basis that no reports targeting this patient population were yet available in the literature. The study enrolled 30 children, 5–9 years old and took place as a summer camp in a resort village in the northern part of Italy with the aim of comparing the AP performance with the pump manually operated by parents [48]. The telemedicine component was still available as a means to preserve patient safety albeit the improved reliability of the AP rendered it almost redundant. Given the subject population of the study, an additional perspective for the remote monitoring component was investigated this time, considering it as a means of overseeing children by their parents and reassuring them [49]. Thus, in this case, parents become the main stakeholders of the telemedicine system.

3. Results

Following the classification proposed in [22], the two active telemedicine systems just described can be both classified in the highest risk group (D). The authors chose the most representative example functionalities of class D applications to be precisely clinical decision support (as in MobiGuide) and closed loop control (as in AP@home). In this result section we summarize the main functionalities we identified as responsible for the most relevant risks, in the effort to create a list of known criticalities that can be generalized to other telemedicine systems implementing similar features. We also describe possible strategies able to mitigate the identified risks and, in the following discussion section, briefly comment upon the European legal framework surrounding the specific responsibility and liability issues. Table 1 reports the list of features, associated risks and responsible stakeholders we were able to identify from our two example use cases.

In the following, we elaborate on the features presented in Table 1.

3.1. Feature 1

Regardless of their computerization, legal implications of clinical practice guidelines have been debated for some time [50,51]. Physicians may prefer to fully comply with guidelines in order to have a justification for every action they do and patients may complain if something goes wrong and they realize that the treatment received is not compliant with guidelines. Computerization and distribution of decision support through telemedicine and homecare systems add some specific issues. When formalized and executed by a computerized system, guidelines are often considered by physicians too rigid to account for the personalization of the treatment that is often needed to account for the peculiarities of the specific patient at hand. However some of the most advanced systems, like MobiGuide, formally take into account the patient context and personalize the guideline execution accordingly [52]. Similarly, also shared-decision making between patient and physician is also supported by the system[53]. Another aspect

Table 1
List of features, associated risks and potential responsible stakeholders.

	Features	Associated risks	Potential responsible stakeholders
MobiGuide	1. Based on Computer-interpretable guidelines	Errors in the formalization	knowledge engineer, physician (domain expert)
		Has to be kept up-to-date	knowledge engineer, physician (domain expert)
		Legal implications of clinical guidelines alone	physician
	2. Clinical recommendations automatically generated by the system	DSS engine can malfunction	system developer
	3. Patient is actively involved in decisions	The patient assumes more responsibilities about his own health and maintenance of the system	patient, physician
	4. Reminders for pharmacological medications	Deal with exceptions (phone off, drug-drug interactions, did the patient actually take the pill?, etc.)	physician, patient, system developer, knowledge engineer
		Wrong indications can harm the patient	physician, patient, system developer
AP@home	5. Data coming directly from patient interfaces/devices	Data transmission problems	system developer, hospital administrator (provides the hardware), hardware vendor (for defective hardware), communication service provider
		Wrong data inserted by the patient	patient, system developer
		Low quality of data	patient, system developer, hardware vendor (if a sensor is underperforming/malfunctioning)
	6. Real-time remote monitoring	Remote monitoring might engage physicians/nurses 24/7	physician, nurse, hospital administrator
		Wrong interpretation of data	physician, nurse
		Delays in data availability/data loss	system developer, network service provider
	7.Closed-loop control of vital parameters	Wrong amount of medications may be administered	system developer (model developer and control alg. developer), hardware vendor (if actuators or sensors malfunction)
		Sensor needs to be calibrated periodically	patient, physician, nurse
		Risk of unmanageable events (e.g. hypoglycemia needing a glucose bolus)	patient, physician
	8. Target vulnerable patients	Risk of harming patients that are not aware of all the risks/cannot "take over" system control (e.g. fetus in GDM and pediatric T2D patients)	patient, physician

to consider when dealing with guideline-based systems concerns liability and system errors: who's liable if a computerized clinical practice guideline provides an erroneous recommendation? Guideline recommendations are often written with an ambiguous phrasing. In this case, their interpretation is an issue. While the guideline text remains on paper, every physician gives his own interpretation. But when a guideline is computerized, somebody disambiguates the text and decides for one precise interpretation [54]. Errors can occur in this process leading to the implementation of a definitely wrong interpretation. Usually this process is carried out by medical experts and knowledge engineers, thus responsibility, in principle, should be shared among them. On the other hand, guideline text is sometimes ambiguous in itself: e.g. "Prescribe drug F in presence of the symptoms S1, S2, S3", may be interpreted as "all the 3 symptoms" or "at least 1 out of the 3 symptoms". Note that people in charge of the formalization of a guideline may even not realize the presence of such an ambiguity, and uncover it only during a discussion with colleagues. Therefore, a possible mitigation action consists in a peer-review process for each computer-formalized guideline. Of course this implies to look for methods able to show the actual formalization to people not familiar with computer code. Formal flowcharts, with clear labels and annotations, could be a suitable mean. A few other solutions for the issue have been proposed in the literature such as following a strict knowledge acquisition process for guidelines [55] or merging the guideline development and formalization stages into one simultaneous process to minimize discrepancies [56]. Feature 1 also deals with guidelines maintenance. If a new version of the guideline is delivered, the computerized version should be updated as well. If not, obsolete recommendations could be generated. For risk mitigation, the authors of any computerized guideline should clearly declare its maintenance plan.

3.2. Feature 2

While formalization is a joint task of medical experts and knowledge engineers, only technical people are involved in the development of the inference engine that generates the actual recommendations that reach physicians through their interface. As for any software tool, it could be affected by bugs. Simulation studies, generating recommendations for a set of fake patients, validated by medical experts, could be a useful mitigation action.

3.3. Feature 3

Patients are actively involved in the management of their device when using telemedicine to improve the self-management of their condition. As a consequence, they should take care, for example, of the good state of their smartphone (e.g. maintain battery charged, check the wifi functionality, do not download other apps that could interfere with the healthcare app, etc.). To mitigate the risks, a proper training phase is necessary for patients. During the training phase also responsibilities of the patient her/himself while using the system must be clearly stated and, to minimize risks, patients not willing/unable to assume those responsibilities should be excluded from the use of active telemedicine systems.

3.4. Feature 4

Drug reminders are one of the most common functionalities of healthcare apps. There is a great variability about the way these apps generate reminders, but to our knowledge, no one deals with the issue of a missing reminder due to the fact that the smartphone is turned-off. In general, those missing reminders are simply ignored. However, a patient could complain if a reminder is not delivered, say, due to a few seconds of smartphone power interruption. Potential risk of harming a patient is high in the cases where medications are involved. For mitigating such a risk, patients should be clearly informed about the

limitations of the system regarding drug reminders (does the system check for interactions? Does it automatically manage deviations from predefined plans?) and be instructed on proper actions to take if they feel a recommendation they are receiving is wrong (e.g. never take a double dose without consulting your doctor first, even if the system suggests to do so). Extra caution should be paid when the target users of medication reminder systems consist in elderly or cognitively impaired patients. On the one hand this population is the one most likely to benefit from medication reminder support, but careful design of such systems (e.g. accessible user interface, clear and concise text for reminders to avoid confusion, ease of use etc.) is required to provide an adequate level of safety. Improving the reliability of drug reminding systems is, to our best knowledge, still a largely unaddressed challenge and responsibilities are often delegated to the patients using the systems.

3.5. Feature 5

Home monitoring systems are mostly based on trustiness of patients. This creates the possibility for patients to enter wrong data, either unintentionally or on purpose (e.g. to pretend to be in good weight control and avoid stricter diet). The possibility of persons other than the patient using the smartphone also needs to be taken into account. Furthermore, reliability of data communications is essential. If an ECG signal must be sent to a doctor in order to detect arrhythmia episodes, which can be very short in time, it is very important that the signal is transmitted entirely. A doctor could be concerned about legal implications of any delay or loss of data during transmission (what if a potentially significant event is lost or a diagnosis of an urgent condition is lost for this reason?) as well as for degradation of data quality that might impede their correct interpretation. Recent work highlighted the crucial role of data quality and technological context assessment components in mitigating such risks [57,58].

3.6. Feature 6

Some physicians would like to receive e-mail or even sms when alerts are “critical” (e.g., fever that could indicate sepsis from neutropenia in a cancer patient). Others have argued that this would lead them to “be available” or at least “feel responsible” 24 h. If a doctor, during the weekend, the night, etc., receives important information for patient health through a computerized system, is he obliged to look at that information and act accordingly? Is it correct that this choice is up to the physician? Or should the DSS notify the hospital, where somebody will redirect the request to the doctors on duty? This feature calls for considering organizational changes induced by the introduction of technological innovations such as DSS to mitigate these risks. Systems providing real-time (or almost real-time) remote monitoring of patients are also subject to the criticalities regarding data loss, transmission problems and data quality highlighted for feature 6.

3.7. Feature 7

Closed loop control of vital parameters is a particularly critical feature. The main risk obviously derives from the fact that the system autonomously performs actions to keep the patient in good health status while running potentially unattended. This is the case of the AP@home where insulin may be delivered through a pump to a patient experiencing rising blood glucose levels. A proper maintenance of the sensors and actuators involved in the automated system is crucial to avoid malfunctioning and, once again, patient training is essential here. Remote surveillance by physician users adds a further level of control and mitigates the risks. Collecting longitudinal data on a central server would enable the discovery of remarkable trends that develop over longer periods of time. For example, analysis of a blood glucose time series may detect a decrease in sensitivity to insulin in a diabetic patient and dynamically send a new set of parameters to the controller on the patient wearable device to correct this effect. However, the risk of events that may not be manageable by the system alone still persists. For example, this is the case of hypoglycemia: despite the AP@home system is able to deliver insulin to control high blood glucose levels, it cannot provide glucose in case of a hypoglycemia. The responsibility of managing such events is still delegated to the patient, which must be properly trained and aware of the limits of the system.

3.8. Feature 8

A final remark regards those systems that target particularly vulnerable patient populations. This occurred in both our use-cases: Mobiguide was used by pregnant women with GDM and AP@home was tested on a small pediatric population. These groups of patients can be deemed vulnerable for different reasons. GDM can directly affect both mother and fetus [59] who, for example, can grow overweight due to high blood glucose levels or be at a higher risk of developing type 2 diabetes later in life if the GDM was not properly managed. Concerns about the eligibility of minors to be users of such systems may arise, given the fact that they may not be fully aware of the involved risks and they can’t autonomously decide whether to accept those risks. For these reasons, parents and significant others must be involved in these decisions, and ultimately carry the full responsibility. It is important to note that, however, the use of active telemedicine systems is rarely extended to these vulnerable classes of users, apart from a few experiments usually conducted in a controlled research setting [60].

4. Discussion

When exploring legal issues involved in telemedicine the preliminary question is how to legally define the particular type of device or software we are focusing on.

A first possibility is to consider the telemedicine system as a consumer good, as such being regulated by the Directive 1999/44/EC on the sale of consumer goods.[1] The main requirements in this sense are that “Consumer goods must be in conformity with their contract of sale” and “Goods are deemed to be in conformity with the contract if, at the moment of delivery to the consumer, they (Article 2):

(a) “comply with the description given by the seller and possess the qualities of the goods which the seller has held out to the consumer as a sample or model;
(b) are fit for any particular purpose for which the consumer requires them and which he made known to the seller at the time of conclusion of the contract and which the seller has accepted;
(c) are fit for the purposes for which goods of the same type are normally used;
(d) show the quality and performance which are normal in goods of the same type and which the consumer can reasonably expect, given the nature of the goods and taking into account any public statements on the specific characteristics of the goods made about them by the seller, the producer or his representative, particularly in advertising or on labelling.”

The seller shall be liable to the consumer for any lack of conformity that exists at the time the goods were delivered. All of these provisions surely apply also to a device with specific medical apps.

When a software, as in the case of Mobiguide and AP@Home, has medical purposes, however, it becomes crucial to define whether it can

[1] The purpose of this directive is the approximation of the laws, regulations and administrative provisions of Member States on certain aspects of the sale of consumer goods, such as robots, and associated guarantees in order to ensure a uniform minimum level of consumer protection in the context of the internal market.

be specifically qualified as a medical device.

This legal definition, in fact, represents the fundamental precondition for identifying the set of rules to be applied. The main point of reference in Europe is the Medical Devices Directive (93/42/EEC), adopted by the Council of the European Communities on 14 June 1993.[2] According to this regulation, while a software embedded or incorporated into a medical hardware is already part of the medical device, a "standalone software", such as the one used in mHealth apps, can be considered a medical device and falls under the scope of the Directive only if it has a "medical purpose".[3] Conversely, a stand-alone software intended for general purposes is not a medical device, even when it is used in a healthcare setting.[4] The Directive also clarifies that the software is intended for medical purpose if the manufacturer intended human beings to use it for purposes of: (a) diagnosis, prevention, monitoring, treatment or alleviation of disease; (b) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap; (c) investigation, replacement or modification of the anatomy or of a physiological process; or (d) control of conception.[5] More recently the European Commission issued a set of Guidelines on the qualification and classification of standalone software (issued in January 2012 and recently updated on 15 July 2016) according to which the decisive criterion is related to whether the software is intended to interpret (or to facilitate the interpretation of) data by modifying or representing health related individual information. The software has to perform an action for the benefit of individual patients: for example, it is intended to be used for the evaluation of patient data to support or influence the medical care provided to that patient.[6] Thus, an mHealth app would not be a medical device if it merely performs an action limited to storage, archival, communication, 'simple search' or lossless compression.[7]

Despite these efforts, the criterion of the "intended medical use" is not always straightforward. In this sense, the distinction between "wellness" apps and "medical" apps may become unclear, since the preventive and self-monitoring activities carried out by the former may significantly improve health outcomes.[8] In 2016 the EU finally reached an agreement on updates to the overarching regulations for medical devices and in vitro diagnostics.[9] A fundamental revision of those Directives is needed to establish a robust, transparent, predictable and sustainable regulatory framework for medical devices that ensures a high level of safety and health whilst supporting innovation.[10]

The draft regulations declared the following purposes: i) tighten the regulation and surveillance of notified bodies, the independent entities responsible for assessing medical devices before they can be marketed; ii) establish how manufacturers will be responsible for tracking the quality, performance and safety of devices; iii) improve the availability of clinical data on devices and strengthen the protection of patients participating in device trials; iv) create a Medical Device Coordination Group comprised of national representatives that will double check assessments of high-risk devices carried out by notified bodies before the devices are placed on the market; v) create a central database to track economic operators, notified bodies, market surveillance, vigilance, clinical investigations and certificates.[11]

Within the mentioned regulations, we can now attempt to draft a legal framework for Mobiguide and AP@Home. The first step is defining whether they are medical devices.

4.1. Mobiguide

the system is based on a combination of clinical practice guidelines and patient data, inserted by patients themselves and possibly by physicians. In addition, clinical data might flow from the hospital EMR to the integrated personal health record. The outputs are recommendations for the patient (to take measurements; medications; diet prescription, etc, …) and for the physician. The pilot implementations have been designed for patients with atrial fibrillation or gestational diabetes mellitus diseases.

The described approach falls within the provision that "the software has to perform an action for the benefit of individual patients: for example, it is intended to be used for the evaluation of patient data to support or influence the medical care provided to that patient". As such, the device does not merely perform an action limited to storage, archival, communication, 'simple search' or lossless compression. Thus, it could be considered a medical device.

4.2. AP@Home

The device was assembled starting with certified medical devices such as a blood glucose meter operating in real time and an insulin infusion pump. Those were managed by the patient as separate components in the standard therapy. Then a smartphone was added linked to those devices encapsulating both the control logic for automating insulin administration based on the actual blood glucose levels and the remote monitoring component. Several trials have been conducted also enrolling paediatric patients; in those cases the use of the device was mainly performed by their parents. The overall features of this software and device make it fall under the scope of medical device definition.

The second level of analysis concerns liability. Assuming that an e-medical device is successfully tested in a clinical trial and put into the market, and assuming that hospitals start to use it for their patients, the most common struggle within the medical community is about who can be deemed liable in case of damages occurred to the patient during use of the device (out of the hospital).

Some preliminary considerations are about the first steps to be followed by producers. A first verification could be about the safety and usability of the device. A good example of general correct behaviour at a European level (we must specify that each EU member state can have more specific regulations) is described by the Guidelines on Medical Devices released in December 2009 by the European Commission. It states that, when placing a medical device on the market, the

[2] In the EU, medical devices are regulated under this Directive (93/42/EEC), Active implantable medical devices Directive (90/385/EEC) and the In Vitro Diagnostic Medical Devices Directive (98/79/EEC). Attention will be focused on the former, the latter being less relevant for the aim of this paper.

[3] Recital 6, Medical Devices Directive. "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."

[4] In the Green Paper on mHealth, published in April 2014, the European Commission (EC) explained that mHealth covers "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices," as well as "applications such as lifestyle and well-being apps as well as personal guidance systems, health information and medication reminders provided by sms and telemedicine provided wirelessly." This broad definition thus entails two categories of health related apps, which are broadly called mHealth apps (although the distinction is not always straightforward): (a) apps for the purpose of prevention, diagnosis and treatment of diseases (medical apps); and (b) apps relevant to lifestyle, fitness and well-being (nonmedical apps).

[5] Article 1 (2) (a) of the Medical Devices Directive (93/42/EEC).

[6] Guidelines, p. 12 Decision Step 4.

[7] Guidelines, p. 11, Decision Step 3.

[8] Guidance on borderlines with medical devices were issued by the European Working Group on Borderline and Classification and by the Medicines and Healthcare Products Regulatory Agency (MHRA).

[9] Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 (2012/0266 (COD)) and Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices (2012/0267 (COD)).

[10] Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, Whereas 1.

[11] See more at: http://www.raps.org/Regulatory-Focus/News/2016/05/25/25017/Updated-EU-Reaches-Agreement-on-New-Medical-Device-IVD-Regulations/#sthash.7Z4ekf3y.dpuf.

manufacturer should adhere to the following steps: (i) identify the essential requirements that require support from relevant clinical data; (ii) identify available clinical data relevant to the device and its intended use; (iii) evaluate data in terms of its suitability for establishing the safety and performance of the device; (iv) generate any clinical data needed to address outstanding issues; (v) bring all the clinical data together to reach conclusions about the clinical safety and performance of the device. The results of this process should be documented in a clinical evaluation report. The clinical evaluation report, and the clinical data on which it is based, serve as the clinical evidence that supports the marketing of the device.

These premises merge with the necessity of the appropriate CE marking. A medical device (MD) may be classified as Class I (including Is & Im), Class IIa, IIb and III, with Class III covering the highest risk products.[12] It is usually the "Intended Purpose" of use that determines the class of the medical device rather than its technical features.

Once the device has all the required certifications, if damage occurs to patients, the liability will be determined according to the type of event. With regard to devices like MobiGuide and AP@home, these scenarios can be outlined as follows:

a) Recommendation to the patients caused by errors in formalization of the clinical guidelines, or to the choice of not-updated guidelines or not feasible for the specific characteristics of the patient. In this case, guidelines might be formalized at a national level[13] or generally considered recognized at the international level. A first set of problems is that guidelines tend to be vulnerable to rapid obsolescence, are often vague, and sometimes are written by authors with conflicts of interest. If the chosen guidelines are not updated or are not the correct ones for a specific case, and the recommendations given to the patients follow this wrong indication, the responsibility will be on the person who implemented them (the physician or the manufacturer). In legal systems like the Italian one, the Minister of Health periodically publishes recognized clinical and medical guidelines: the implementation of this kind of guidelines rather than that of different ones can be a substantial means to demonstrate the correct behaviour in programming and updating the device.
b) The system suffers any kind of malfunctioning and these problems were reasonably recognizable by the hospital where the patient was given the device. In this case, the hospital might be deemed liable for not reporting the inadequacy of the device, as well as the producer for putting into the market a defective product.
c) The system has no technical problem but the patient incorrectly inserted his/her (medical or personal) data. In this case, the verification of facts can be more difficult. In general, the patient should be correctly informed in advance about how to handle the device and, with the highest level of detail, about how to interpret and insert his/her data and the recommendations given by the device. The above mentioned Proposal for a Regulation of the European Parliament and of the Council on medical devices, provides that "devices for use by lay persons shall be designed and manufactured in such a way that they perform appropriately for their intended purpose taking into account the skills and the means available to lay persons and the influence resulting from variation that can reasonably be anticipated in the layperson's technique and environment. The information and instructions provided by the manufacturer shall be easy for the lay person to understand and apply".[14] The legal focus here would then be on the possibility for the patient to understand how to use the device and the distribution of responsibility between the patient her/himself and the physician/nurse who possibly had the burden to periodically check the conditions and the functioning of the device.

Looking at the future, an important innovation in this technological landscape is a new generation of adaptive ("intelligent") devices. These devices can learn over time, according to the data provided by the patient and by the physician. In the past, a manufacturing defect had a "stable" dimension, but now we can hypothesize the existence of a spectrum of responsibility. In particular, if the functioning of autonomous systems also depends on data input by the user, the patient could be found more liable for damages the longer the time that has passed since he started using the device. In other words, the patient's responsibility would increase over time.

5. Conclusion

In this paper we identified and discussed some critical features of active telemedicine systems that pose relevant challenges regarding patient safety, and liability of the involved stakeholders. We derived our considerations from our experience in two specific projects and two workshops. The list of risks associated with active telemedicine systems we provided might thus be non-exhaustive and might be integrated by future research. However, a good part of our findings are general enough to be applicable to other active telemedicine systems characterized by similar features. Further studies are needed to develop strategies to counteract the identified risks.

In the discussion section we also gave a brief overview of the relevant European legal framework that regulates this class of systems, providing pointers to specific norms and highlighting possible liability profiles for involved stakeholders if one of these systems transitioned from the research stage to the market. It should be noted that, in addition to the European regulatory framework, also local legislation (national or sub-national) and the coordination of different regulations (e.g. national vs. European, or national vs national in the case of international projects) play a pivotal role in defining legal challenges for telemedicine systems. A limitation of the article consists in our choice of leaving data privacy and confidentiality issues out of scope, since an in-depth analysis of the topic would require a dedicated article and a fair amount of research on the topic is already available in the literature [10,16].

Patients are more and more willing to adopt telemedicine systems to improve their ability to self-manage while feeling safe thanks to the monitoring and guidance provided by such systems [36,61,62]. However, a determinant factor for a broader adoption of these systems consists in increasing their compliance with existing regulations and better define responsibilities and liability profiles for all the involved stakeholders: patients, physicians and nurses, system developers, hardware vendors and hospital administrators.

Authors' contributions

E.P., E.L., G.L. and S.Q. wrote the introduction, methods and results sections of the manuscript. The same authors were directly involved in the AP@home and Mobiguide projects on which this article is based on. B.B. and M.T., with the supervision of A.S., wrote the discussion section focusing on the European legal perspective and relevant regulations. R.B., S.Q. and G.L. reviewed the article and supervised the study. All

[12] All Class Is, Im, IIa, IIb and III medical devices require the intervention of third party: the so-called Notified Body. The higher the classification the greater the level of assessment required of a medical device will depend up on a series of factors, including: (a) how long the device is intended to be in continuous use, (b) whether or not the device is invasive or surgically invasive, (c) whether the device is implantable or active, (d) whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device.

[13] In Italy, the list is published by the Minister of Health.

[14] The Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009.

authors were involved in the workshops from which the article originated.

Statement on conflicts of interest

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Summary table

What was already known on the topic

- Telemedicine systems can improve self-management and are often well accepted by patients
- Systems that offer more than simple telemonitoring functionalities may bring relevant risks to patients
- Legal and regulatory framework is one of the main factors influencing success of telemedicine applications

What this study added to our knowledge

- Analyzing those features offered by a telemedicine system that allow an active, non-mediated interaction with patients can help identifying the most relevant risks and corresponding mitigation strategies.
- Additional stakeholders to the traditionally considered patient and physician need to be factored in the analysis: nurses, system developers, knowledge engineers, hardware vendors, communication service providers and hospital administrators.
- Clearly delineating the liability profiles of all the involved stakeholders can help avoid defensive medicine practices and barriers to a broader adoption of telemedicine.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijmedinf.2018.01.012.

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