The regulation of mobile medical applications

Ali Kemal Yetisen,*[a] J. L. Martinez-Hurtado,[a] Fernando da Cruz Vasconcellos,[a] M. C. Emre Simsekler,[b] Muhammad Safwan Akram[a] and Christopher R. Lowe[a]

The rapidly expanding number of mobile medical applications have the potential to transform the patient–healthcare provider relationship by improving the turnaround time and reducing costs. In September 2013, the U.S. Food and Drug Administration (FDA) issued guidance to regulate these applications and protect consumers by minimising the risks associated with their unintended use. This guidance distinguishes between the subset of mobile medical apps which may be subject to regulation and those that are not. The marketing claims of the application determine the intent. Areas of concern include compliance with regular updates of the operating systems and of the mobile medical apps themselves. In this article, we explain the essence of this FDA guidance by providing examples and evaluating the impact on academia, industry and other key stakeholders, such as patients and clinicians. Our assessment indicates that awareness and incorporation of the guidelines into product development can hasten the commercialisation and market entry process. Furthermore, potential obstacles have been discussed and directions for future development suggested.

Introduction

Mobile Health, also known as mHealth, is defined as the use of wireless communication to support efficiency in public health and clinical practice.[1] To facilitate mHealth, mobile applications (apps) have been developed, which can be executed either on a mobile platform (*i.e.* a 'handheld commercial off-the-shelf computing platform', with or without wireless connectivity) or on a web-based software application that is tailored to a mobile platform but is executed on a server.[2] Mobile medical apps are accessories to a regulated medical device or are software that transforms a mobile platform into a regulated medical device.[3] These mobile devices may include, but are not restricted to, mobile phones or smartphones, tablet computers, smartwatches and point-of-care devices.

As mobile phone penetration worldwide is growing at an increasing pace (7 billion subscriptions as of October 2013),[4] mHealth represents an unprecedented opportunity to increase efficiency and reduce costs in the healthcare systems, both in developed and emerging nations. There are three major categories where mHealth may find applications. First, preventive medicine and health promotion can be leveraged through education and awareness applications. Secondly,

portable diagnostic devices may allow the monitoring of human conditions in clinical settings or offsite locations. Portable devices as a digital assistant may assist clinicians to access reference information to support diagnostic decisions or be used as a screening test for metabolic disorders and infectious diseases. They could also be used to provide support for adherence to treatments. An attractive attribute of the mobile devices is that they may provide real-time data surveillance, which may be useful in the timely reporting of disease outbreaks (*e.g.*, epidemics), disasters and accidents.

Other applications include data management, training medical personnel and mobile payments.

Despite the high potential for improving healthcare, mobile medical applications, if misused or misinterpreted, can provide erroneous diagnosis, and therefore pose a risk to the general public. The United States Food and Drug Administration (FDA) oversees medical applications and assesses their potential misuse or malfunction in order to reduce these risks to the public. This growing risk factor prompted the FDA to introduce a draft guidance in 2011.[5] Recently, in September (2013), the FDA released its final guidance entitled "Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff".[2] Although this guidance resembles the 2011 draft, it lays out the clear distinction between an unregulated "mobile application" and a "mobile medical application" subject to overt FDA regulation. This guidance focuses on apps that possess a greater risk to patients if they don't function as they intended.

Here, we provide an overview of the new FDA regulations for mobile health application development, evaluate its

[a] *Department of Chemical Engineering and Biotechnology, University of Cambridge, Tennis Court Road, Cambridge, CB2 1QT, UK.*
E-mail: ay283@cam.ac.uk; Tel: +44 (0) 1223 334162
[b] *Department of Engineering, University of Cambridge, Trumpington Street, Cambridge, CB2 1PZ, UK*

impact from multiple perspectives (*i.e.* regulators, academics, developers, clinicians and patients), and discuss its implications on the emerging markets (Fig. 1).

Regulatory agencies

The FDA intends to regulate the applications that pose a high risk to the public and it has put aside existing uncertainty[6] regarding applications which would come under regulatory
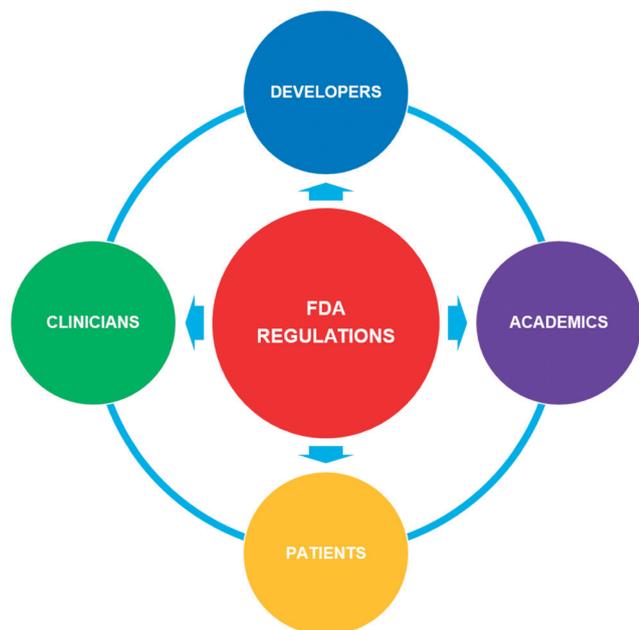

Fig. 1 The shareholders of mobile medical applications.

preview. However, enforcement discretion lies with the FDA. It is important to understand that only applications that transform a mobile phone or any other electronic device into a medical device are eligible for consideration for regulation. These are the medical devices that already come under section 201(h) of the Federal Food, Drug, and Cosmetics Act.[3] However, regulators will keep a close eye on the applications that seek to replace a doctor's visit or perform some sort of clinical test, for example, the new mobile phone app 'SpiroSmart'[7] which has been developed to measure lung function by blowing on a mobile phone, thus turning the phone into a spirometer. This is very helpful for patients with chronic obstructive pulmonary disease (COPD), who were previously reliant on going to the clinic and blowing into a tube with a turbine to measure the flow speed. Similarly, all applications that are likely to perform clinical tests, for example blood/urine analysis, would still require approval; for example, uCheck Universal is a urine analyser, which integrates with a phone, thus turning it into a medical laboratory.[8] For all such companies, a proper 510(k) application will be required, and claims like "as good as centralised laboratory equipment" would require some backing up with clinical data. Table 1 lists the categories to which the FDA plans to apply regulatory oversight.

Medical health companies are not only innovating in the technology arena, but also in business and regulatory systems. One tricorder manufacturing company, Scanadu,[9] is using crowd funding to fund FDA approval for two of its products namely Scanadu Scout™ and Scanaflo™; moreover, they are asking consumers to send data to help them with clinical studies. However, the health apps targeting mass markets and claiming general health benefits, such as apps

Table 1 Categories of mobile medical application by the FDA[2,11]

Applications functionality	Example	Consideration
As an extension of approved medical device including displaying, storing, analysing, or transmitting patient specific data	Display of medical images X-rays and MRI, graphic data such as EEG waveforms, bedside monitors	High risk Good resolution of the screen is extremely important in certain cases like X-ray/MRI as lower resolution may affect clinical decision negatively
Applications that convert a mobile platform into a medical device	Converting phone/smart watches into urine-analysers or glucometers	High risk
	Attachment of transducers to make stethoscopes, spirometers	Readings may directly affect the clinical decisions; therefore apps need to be extremely accurate. Marketing claims will also determine whether products fall under the regulatory regime or not.
Applications/websites diagnosing & recommending treatment options on the basis of patient specific input	Prognosis of the disease, treatment options, dosage calculators	Medium risk The geographic region is very important. If a drug is not available over the counter and patient needs a prescription then its low risk. However, if any such program miscalculates a serious condition to be a minor one then it may be lethal for the patient.
Apps for general health applications & education purposes	BMI calculators, heart rate monitors	Low risk
	Thermometers, medication reminders, personal health record systems, body fat calculators	Marketing claims are critical for products to be placed in general health benefits category which is a very low risk, most health applications for mass public consumption are likely to fall under this category. The FDA does not intended to regulate medical text books and various student aids for examination preparation.

regarding weight management and general cardiac function, might not come under FDA review. The marketing material will be very important in this regard as it determines the intended use of the device; if any device asks its user to make a decision on his/her treatment, then it would definitely fall under a review, but if it provides information about some vital body sign and advises you to seek medical attention, then an oversight might not be required. To date, the FDA has approved around 75 medical health apps, 25 of which were passed in the last 12 months.[10] It does not aim to regulate any of the application market spaces like Apple App store, Google Play or Happatique. It is important to note the extent of clinical decision support that these apps provide. There is one challenging area, which the FDA would need to address, and that relates to the upgrading of the approved mobile applications. Operating platforms frequently change and different application providers constantly upgrade their apps to remove any functional glitches that may occur. In medical devices, if any device manufacturer has to alter their device to improve performance they have to go for the '510(k) special' approval pathway, which is an accelerated version to get the products faster to market. However, even if a similar pathway is provided to application developers, it will be too slow for the app manufacturer. By the time an improved version of the app gets approval, the mobile platform would have changed again.

Academics and researchers

Researchers, scientists and engineers working with mobile healthcare apps should be concerned with the implications that the new FDA guidance will have on their research and development strategies. Clear understanding of these regulatory guidelines is of utmost importance for the rational planning and development of practical, compliant and real world mobile medical apps.

Many academic groups have dedicated effort to develop mobile healthcare apps and devices.[12–21] Prof. Ozcan's research laboratory at the University of California-Los Angeles that specialises in biophotonics has spun out the company Holomic LLC in 2011 to commercialise smartphone-based applications for point-of-care, telemedicine and public health monitoring.[22] Research and development for Holomic has been primarily funded by governmental agencies such as the National Science Foundation (NSF), the National Institutes of Health (NIH), the Office of Naval Research (ONR) and the Army Research Office (ARO).[13–17,22] Similarly, Prof. Copper's research group at the University of Colorado-Boulder, has also spun out a company, Mobile Assay Inc., to address medical diagnostic challenges through the development of mobile rapid diagnostic test readers.[23–25] The company has received funding from the Bill & Melinda Gates Foundation as part of the Grand Challenges Exploration Initiative, primarily to develop a low-cost, highly sensitive smartphone-based platform to image and amplify signals from immunoassays to detect infection caused by fungi (*i.e. Botrytis cinerea*,

Aspergillus flavus) in plants and aflatoxins in seeds or the environment.[25] Mobile Assay claims that their apps are capable of quantifying lateral-flow assays with enhanced sensitivity.[25] In startup companies from academia, the research groups need to work closely with the FDA in order to meet the requirements of the recent regulatory guidelines.

Lack of knowledge and experience with the regulatory process represents a barrier for moving a mobile medical device out of the research lab and into the clinic. Indeed, a general consensus among academics is that collaborative problem-solving between academics and the FDA will need to be well established and organised.[26] To achieve this, medical device technology innovation partnership forums have been organised.[26,27] These forums discuss innovation technology transfer and scientific interchange in order to leverage academic and FDA collaborations to create solutions for pressing public health challenges. In these forums, learning experiences about medical device regulatory curricula are shared and unmet needs identified.[28] These educational programs play a critical role in device development and assessment, and also help academia with regards to the regulatory development process. For example, hands-on exercises such as case studies to teach and practice regulatory concepts and processes can greatly benefit the academic community. The FDA has published its two first Harvard Business school-type case studies involving a fledgling company working to bring its first medical healthcare application to market. The first involves advising on the best regulatory pathway available,[29] while the second study addresses safety assurance and risk mitigation.[30] In addition, these case studies can involve experimental learning through mock 510(k) and 513(g) studies.[31–34] Furthermore, FDA courses can be incorporated into existing academic curricula, which may involve design controls, regulatory pathways and quality status reports. These courses should be offered across the board from early undergraduate students to professors. Notably, students, in most academic institutions in the US and in Europe, are allowed to own the intellectual property rights to their innovations. Exposure to studies involving regulatory processes is necessary because this will promote enthusiasm, research drive and innovative thinking. Such studies can help with defining the terminology, categorising the device type under FDA classification, identifying protocols to follow for market approval and clearance, generating status reports of the marketed device, and evaluating business risk and strategy. Moreover, these programs can provide a database of devices which can be ordered based on risk, timeline of the clearance, and costs.

The Vice-Chancellor of the University of Cambridge, Professor Sir Leszek Borysiewicz, is of the opinion that 'regulatory bodies must employ a strong evidence base to support the standards they impose and those involved in applied research and technology transfer should be committed and well informed about the risks and regulations.' He furthermore stated that 'it is important that funding agencies and academics are prepared to engage in research to support regulation.'[35]

Strong collaboration between academics, funding agencies and regulatory bodies bodes well for the future. For this, specific points of contacts between the different shareholders, along with efficient cross-communication, will be required. There are numerous foreseeable benefits that will result from this joint effort – from safer devices and therapies to fast implementation of practical solutions for some of the world's most pressing healthcare problems.

Developers and entrepreneurs

Innovation can only happen when there are no restrictions on imagination. Developers crafting ideas to revolutionise the healthcare market with mobile apps have encountered certain limitations in the past after the FDA has taken a serious position, for example, issuing a warning letter to Biosense about their compliance.[36] Even though not all apps require FDA clearance, developers perceived this as a global limitation for innovation.[37] Apps that were claiming diagnostic capabilities, which they were able to do, soon found that the regulations around these claims did not exist to promote freely those features.[36] One of the important lessons of the early warnings was to limit the claims of the mobile apps to the actual benefit provided to the user. Also, prior to further development, research for legislation that may limit the use of an app could prevent barrier warnings.

As more mobile apps were developed, the discussion between the regulatory authorities and developers also increased (at least in the US). Thus, the developer's view of the regulatory paths for mobile healthcare applications changed from a 'barrier killing innovation' to a platform to market and as a seal of certification of their apps.[37] App hubs were established aiming to provide services emulating traditional medical procedures (i.e. drug prescribing apps); an example of these certification hubs is Happtique.[37] The FDA soon recognised that the 'Entrepreneurs in residence program' could sparkle the linkage between innovation and regulatory agencies.[38] In the particular case of mobile applications, and IT in general, a group was created to promote 'these fresh ideas' for 'lowering healthcare costs' and 'ensuring patient safety'.[39] Experts from several companies representing the early mobile app developers are now discussing regulation of health IT with a focus on priority areas such as meaningful use, quality measures, privacy and security, policy, accountable care, certification/adoption, consumer empowerment, data intermediaries and standards (clinical operations, implementation, consumer technology).[39] Thus, developers and entrepreneurs have a regulatory platform to work alongside continuous innovation. Furthermore, their contributions could well shape the future of mobile healthcare, and besides, with the backup of a regulatory agency, investors may be more willing to fund their ideas without the 'uncertainty' of the issue as in the early days. This panorama of the current mobile healthcare environment for entrepreneurs and developers is constantly evolving. The

Federal Advisory Committee for health IT invites volunteers to join and contribute to the health IT committee; this constitutes an opportunity to shape the future of mobile healthcare from the developer's point of view.[40]

Mobile apps were initially conceived as assistive technology for health professionals including data management, efficient healthcare delivery, collaborative medical teams, telemedicine, remote care for inaccessible areas, and drug prescription and delivery.[41] However, the emphasis of development is now focused on informative apps for end users or patients and on addressing prevalent health conditions. In a recent study,[42] 3673 mobile health apps were found to be related to the top eight medical conditions: iron-deficiency anemia, hearing loss, migraine, low vision, asthma, diabetes mellitus, osteoarthritis and unipolar depressive disorders. Likewise, the study found 247 articles regarding mobile apps for these conditions as of April 2013.[42] The FDA has cleared several mobile healthcare apps since 1997,[43] and with the new guidelines in place, more are expected to gain clearance.[2] This shows the current state of app development; while there are thousands of apps being developed, there are few that need, or are backed up with, scientific research. However, most of them can seek regulatory approval if they fall under the classifications issued by the FDA for mobile medical devices (see Appendix A, B and C of the current regulation (ref. 2)). An example of a step forward in peer-reviewing mobile healthcare apps is set by the NHS (UK) on their health apps library; apps are reviewed to ensure that they are clinically safe before releasing them to the public.[44] Currently, there are 169 apps submitted by developers on the NHS platform, which are now published after the review process and are subject to user rating (Fig. 2). One concern from the developer's point of view is that the timeline for approval is still too long since mobile apps can see new versions in a matter of weeks. Depending on the class type under which the app is classified, the FDA, for example, may take up to 6 months to approve the app.[31] Thus, developers may seek approval for fully developed and tested apps ready for market exposure.

With the 'boom' of home healthcare monitoring, there are numerous players in the app development market and many will probably appear in the following years;[45,46] it is
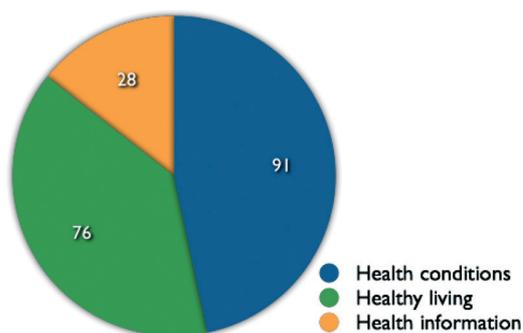

Fig. 2 Health apps reviewed and published on the NHS platform.[44]

estimated that around 1.7 billion mobile device users will have downloaded mobile medical apps by 2018.[47] The FDA evaluates the design and usability of the apps, but soon it will be critical to peer-review the content.[48] Thus, developers must be conscious of this during the app design phase. Collaboration with research institutions, universities and corporations could be a step forward in the efficient peer-reviewing of mobile medical apps.

Patients and clinicians

Around 500 million people will have been using mobile medical applications by 2015; thus, unknown risks can have considerable impact on public health.[49] While mobile medical applications have gained rapid and widespread popularity among clinicians and patients, ensuring that they are safe for use by patients is the top priority to maximise their potential benefits for the healthcare systems.[50] Patient safety is a critical quality dimension in healthcare where many regulations, procedures and policies are available to assure that the healthcare delivery system is safe. Despite these controls, the occurrence of errors in medicine are frequent and common, harming thousands of people around the world every year.[51–54] For example, a study by the Institute of Medicine (IOM) in the US showed that errors in medical practice harm 1.5 million people and kill several thousand people per year in the US alone.[55] While these patient safety issues relate to healthcare settings, the impact of the use of mobile medical apps, whether they worsen or improve the current situation, is still not clear as there is no evidence yet. For example, a study in diabetes has shown that the use of mobile medical applications empower patients to take an active role in managing their own health.[56,57] However, a few studies also highlighted the need for further research on medical applications for diabetes because of the possible risks, such as lack of personalised feedback, usability issues and communication issues between patients and clinicians.[57–61] Due to these possible risks, the FDA will oversee which mobile applications are safe and not harmful if they do not function as intended.[49,50] Hence, there must be a clear indication to assess whether the mobile applications address patient safety.[49,50] The FDA recommends developers to meet the requirements associated with the applicable device classification, which indicates the level of regulatory control needed to assure safety and effectiveness (page 13).[2]

Another approach to address safety concerns is performed by implementing incident reporting systems.[62] In the recent FDA guidance, the Medical Device Reporting (MDR) system is included as a regulatory requirement for mobile medical applications. Such applications are expected to be fully functional and validated before market release. However, in unexpected situations, the MDR requires feedback from users and developers to identify signals of emerging safety problems with the use of mobile medical applications (Appendix E – Section 6).[2] Although developers aim to achieve error-free mobile healthcare applications, in practice, applications may

also pose risks to patients, such as erroneous medical interpretation by patients and software update issues. Therefore, a feedback mechanism is critical to mitigate recurring errors. Moreover, while incident reporting systems are retrospective risk assessment techniques in nature, actions to mitigate errors are taken after incidents happen.[63,64] However, the regulation process may also deploy prospective risk assessment mechanisms that are recommended for use in healthcare settings for patient safety.[54,65] Such mechanisms may become reality in mobile applications to foresee potential patient safety risks before they occur. These can be applied during a mobile medical application development process by prospective risk assessment techniques such as structured brainstorming techniques, which mainly bring key stakeholders such as users, clinicians, application developers and academics together to proactively stimulate what can go wrong with the use of the application.

From the clinician's point of view, the use of mobile medical applications provides a potential means of allowing them to diagnose patients off-site, giving them a chance to access clinical data anytime and wherever they need it.[49,66–70] Although clinicians have highlighted the benefits of mobile medical apps, they have also expressed major concerns regarding their safety and effectiveness.[50] The first concern for clinicians is the lack of their participation and input during the validation process of the mobile application.[50,69] Although initial testing of the application is performed by developers, in general, they have limited expertise in the medical area. For this reason, it is imperative that clinicians provide their input to validate the mobile apps in terms of medical data accuracy and functionality. For example, a study involving orthopaedic applications showed that only about one third of the mobile applications were developed and validated with the participation of clinicians.[50] In another study, the negative effect of the limited involvement of clinicians' was also documented in pain management applications, despite an increasing number of applications being released to market.[71] In order to increase clinicians' involvement during the application development process, two realistic approaches have been proposed. The first approach proposed validation from the clinicians' perspective, whereas the second suggested a certification program to address operability, security and content issues to be evaluated by clinicians.[50] Clinicians as well as patients are also concerned about medical data security. As a crucial aspect and a potential area of risk, security and the confidentiality of the patient data should be securely transmitted and stored in mobile medical applications.[50,67,70,72,73] In parallel with data security, another concern involves update issues, which should abide to Health Level Seven (HL7) and point-of-care testing POCT1-A2 standards.[74,75] Therefore, online medical data inputted by both patients and clinicians must be uploaded regularly and accurately by the application to ensure that it will provide the healthcare benefits for which it was designed for.

Both patients and clinicians are willing to use mobile medical apps to access medical information and healthcare

related tools. Despite potential benefits with the use of mobile medical applications, there are a number of concerns such as usability, communication between patients and clinicians, lack of clinician involvement in the development process, data security and update issues highlighted. Therefore, the regulations should address all these concerns by adopting appropriate solutions as well as ensuring that patient safety is the top priority.

Emerging markets

Developing countries face an increasing incidence of infectious diseases as well as that of non-communicable diseases. Healthcare delivery in resource-poor settings represents a unique challenge due to shortages in healthcare workers and poor infrastructure.[76,77] There are a number of points that need to be taken into account: low literacy and numeracy, limited coverage and the diversity of the languages. Overcoming such challenges may be achieved through the introduction of mobile medical apps. mHealth can remove physical barriers for caring and providing healthcare through creating a leapfrog effect, which bypasses the current centralised approaches in preventive medicine and diagnostics. There are a number of initiatives: InSTEDD, a US-based NGO, provides mHealth-based disease and surveillance solutions in Cambodia. The Canadian development agency, IRDC, has been operating in the Caribbean by providing portable digital assistants to healthcare workers to support decision making and diagnosis. There are also global initiatives launched, such as the United Nations Foundation and Vodafone Foundation Technology Partnership, together with the World Health Organisation (WHO) to distribute their mobile data-gathering program to sub-Saharan Africa. Overall, there are over 50 mHealth projects existing worldwide.[78] For example, an open source software, Medic Mobile offers telemedicine solutions for the management of healthcare information, including data collection, patient tracking, sensing medical data, monitoring drug stocks and patient referrals, analysing data and surveillance of outbreaks.[79] Despite the obvious benefit of such apps, there is a lack of evidence about their applicability in terms of testing and evaluation,[1] in addition to the limited regulations in the developing world.[11] Even though this article focuses on the FDA regulations, pathways to market in other countries have different barriers. For example, companies might have to market versions of their software with the local languages. A potential market of such apps is the developing world, where the regulatory agencies may follow the FDA guidance, but tailor it to their local needs. There is also a need to develop a global regulation guidance for standards involving comparison, cost benefit evaluations, and reproducibility of the design considering sample sizes. For example, guidelines such as ISO/IEC Guide 63:2012 proposed by the International Organisation for Standardisation could be expanded to cover mobile medical apps.[80]

Conclusions

A balance must be struck between ensuring patient safety and providing an ecosystem for innovative app development. These guidelines are critical for entrepreneurs as the marketing claims could determine the fate of their products. However, reimbursement pathways are not very clear especially when two or more companies compete with similar products. The cost and health effectiveness parameters usually applied to drugs are not applicable to software applications. Moreover, the dichotomy between regulated disease-related claims and unregulated health and wellness claims must be clarified. There is a grey area for those developing mobile apps for disease management and health and wellness. More importantly, this guidance does not directly assess the determination of the regulatory classification (Class I or II). It should be expected that device software will be updated frequently and the FDA must clarify if these updates of the software will require overseeing and what regulatory pathway will be applicable. Currently, there is also a clear need for the development of quality systems for mobile medical apps. These quality systems will allow the development of the mobile apps through rigorous design controls, which document and organise the development process. From the global perspective, international standards and regulations must be set to minimise the risk worldwide. Shortly, we expect the European Medicines Agency (EMEA), and the Medicines and Healthcare Products Regulatory Agency (MHRA) to introduce a similar guideline in regulating mobile medical apps in Europe. Likewise, we also anticipate that the Brazilian Health Surveillance Agency (ANVISA), the China Food and Drug Administration, India's Central Drugs Standard Control Organisation and Russia's Federal Service in Surveillance in Healthcare (Roszdravnadzor) will follow a similar path. As the public continues to embrace mobile apps for the management of their healthcare, the providers must act in accordance with the regulations to ensure patient safety.

Notes

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Acknowledgements

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