International mHealth Research: Old Tools and New Challenges

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Background

Nontraditional app-mediated health research is a phenomenon not likely to be restricted to a single jurisdiction. Owing to their increasing ubiquity[1] and processing power,[2] mobile health applications are becoming a powerful tool for both professional and amateur medical researchers.[3] While rates of smartphone ownership remain highest in the most economically developed countries, nearly 4 in 10 adults in emerging economies already reported owning a smartphone in 2016.[4] Globally, rates of smartphone adoption are expected to increase up to 20% by the middle of the next decade, at which point more than 75% of all mobile connections are likely to be made on an internet-connected smartphone.[5] Smartphone applications with health related functions allow users to record biometric data, share symptom reports, and interact with a community of researchers and citizens around the world.[6] For these reasons, they are an increasingly prominent fixture in health research, facilitating connections between traditional and nontraditional researchers alike.[7] As smartphones move rapidly into new consumer markets, such app-mediated research will become correspondingly more international in orientation.

As described elsewhere in this symposium, app-mediated studies carve out a potential role for non-expert "citizen scientists" to contribute to medical research.[8] Much of this research is, in the United States, unregulated. Insofar as citizen-led research is not typically subject to the Common Rule,[9] it falls into an oversight lacuna. And while international app-mediated research surely generates an array of policy challenges, it is not clear that it would face the same regulatory complexity as in the United States. In this paper, we will argue that the idiosyncrasies of the American approach to medical research regulation are not an adequate lens through which to interpret "unregulated" app-mediated studies at the international level.

Below, we will briefly sketch the contours of international app-mediated research. We will describe the two senses in which a study might properly be considered to have an international dimension. From there, we will outline some of the policy challenges facing international app-mediated research. Finally, we will argue that such research is not likely to be excluded from the conventionally applicable regulatory tools at the international level. To be sure, the unregulated status of app-mediated research in the United States is an important, but not decisive factor. We will conclude by proposing further policy attention for these rapidly emerging research practices.

International App-Mediated Research

While the primary focus of this paper is the proliferation of app-mediated studies conducted by non-traditional researchers, the use of smartphones in more conventional research provides useful context for understanding their citizen-led, international expansion. Highly structured app-mediated medical research is presently most prominent among American researchers and institutions.[10] Paradigmatic examples of highly structured app-mediated research

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include the mPower Parkinson's Study, conducted by Sage Bionetworks,[11] and Mole Mapper conducted by researchers at the Oregon Health & Science University.[12] In the fall of 2019, moreover, Apple announced a renewed emphasis on app-mediated research with the launch of three new studies in partnership with the Harvard T.H. Chan School of Public Health, the Brigham and Women's Hospital, and the University of Michigan, among others.[13] A number of existing app-mediated studies, though available only to users of United States app stores, have explicit plans to extend the scope of their research to include international participants.[14] At the same time, increasingly many app-mediated studies in countries other than the United States have been introduced. The Back-on-Track study, for example, was developed by researchers at the University Medical Center Freiberg in Germany to better understand decision making in patients with acute anterior cruciate ligament (ACL) rupture.[15] These trends are indicative of an increasing interest in international app-mediated research, trends we can expect to continue in years to come.

The recent growth of app-mediated research is in large part attributable to the development of open source frameworks for the development of mobile applications capable of facilitating the kinds of research projects described above. In 2015, Apple released ResearchKit, a platform that enables researchers and developers to make study applications available to consumers on the App Store.[16] An Android counterpart, branded ResearchStack, was released in 2016.[17] Together, these research platforms have generated many of the most prominent ongoing app-mediated studies. Neither ResearchKit nor ResearchStack are restricted to institutionally affiliated professional scientists. Both permit nontraditional researchers, including for-profit entities and individual citizens, to conceive and design app-mediated studies; as open source platforms, they are available for anyone to use.[18] This has significantly contributed to the potential growth of nontraditional researchers engaged in app-mediated studies, including at the international level.

There are at least two broad senses in which app-mediated research may be considered "international" in orientation. On the one hand, such research might involve researchers based in multiple jurisdictions working on a common problem and running an associated study on a single application. This is potentially beneficial from an expertise perspective. App-mediated research may be a mechanism with which researchers with complementary expertise can easily collaborate across borders. On the other hand, app-mediated studies may be international to the extent that they seek to recruit participants in multiple countries. Certain studies, for example, might require an especially diverse participant population. App-mediated research promises to simplify the process of recruiting broad, diverse cohorts, a particularly important consideration in the case of research targeted at complex or rare diseases. Of course, many projects will have both researchers and participants in multiple jurisdictions. Our comments will generally apply to each of these categories of international research.

Before moving on, it is worth briefly mentioning that just as there are multiple senses in which app-mediated research may be international, there are also multiple ways in which it might be "unregulated." In the context of this symposium, as we have described, unregulated app-mediated studies are primarily those not subject to the Common Rule. From an interna-

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tional perspective, however, even certain app-mediated studies conducted by traditional professional researchers may raise unique ethical, legal, and policy issues. In particular, the download of study applications is often restricted according to a user's location.[19] But location settings can sometimes be manipulated such that persons located outside of the United States, for example, can access studies ostensibly available only to U.S. residents. In this way, a study subject to the Common Rule in the United States may fall into an uncertain regulatory space if international participants enroll. Though geolocation manipulation for the purpose of illicitly enrolling in research intended to be restricted to residents of a particular country is not likely to become a widespread phenomenon, the possibility of this happening underscores some of the risks of increasingly international app-mediated research. International enrollment might happen whether or not research designers have contemplated this possibility. As the digital world becomes more globally interconnected, it may be reasonable to assume that most app-mediated research will raise international policy concerns.

In the next section, we will detail what some of these concerns may be. We will describe several of the policy issues raised by international app-mediated research and will emphasize how they may be instantiated in the case of studies conducted by nontraditional researchers.

Policy Challenges for International App-Mediated Research

As authors in this symposium and elsewhere have noted, app-mediated research raises a number of novel legal, ethical, and social challenges.[20] Many of these issues will apply equally in the case of international research, though often with an additional layer of complexity. We will briefly examine four such issues: informed consent, privacy, commercialization, and research ethics review. Of course, this should not be interpreted to be an exhaustive list of ethics issues relevant in the context of international app-mediated research. Other issues, such as the return of results and incidental findings, will pose important challenges as well. Instead, the present discussion is meant primarily as a broad overview of an ongoing ethical debate and its implications for app-mediated research conducted internationally.

Informed Consent

Administering informed consent in app-mediated research presents a number of unique challenges.[21] From an ethical perspective, an electronic informed consent process may have certain advantages. Owing to the unique character of the smartphone interface, for example, prospective participants working through an electronic consent form might be prompted to take the consent process more slowly, leading to more careful contemplation of the contours of a study protocol.[22] At the same time, electronically administered consent processes do not usually permit direct engagement with the research team. This limits opportunities for prospective participants to ask questions or receive clarification on elements of the study. To address this, researchers have developed techniques that attempt to address these concerns, for example, by administering quizzes that test the level of a participant's informedness.[23]

In the international app-mediated research context, the challenges presented by informed consent are potentially more acute. Studies that recruit participants in multiple countries, for example, may have to account for vastly different cultural expectations and levels of health literacy than might be expected in a higher income setting.[24] It may be especially challenging for researchers to confirm that prospective participants are informed when both a consent process and associated confirmatory quiz must be designed to account for potentially great cultural difference among participants. Nontraditional researchers may be particularly poorly equipped to manage these considerations. Absent institutional support, for example, the design of a culturally calibrated consent process may be difficult.

Beyond that, there might be a general concern about the adequacy of consent in app-mediated studies conducted by nontraditional researchers. Ensuring that citizen-led studies, in particular, are administering ethically adequate informed consent may be particularly challenging when such research is internationally dispersed. It may be difficult, moreover, to determine which informed consent models are applicable to international app-mediated research. Ensuring that standards are clear and accessible to study designers will be an increasingly complex and critical ethical issue.

Privacy

The protection of user privacy in app-mediated research is another serious ethical consideration. Recent work has found, for example, that smartphone applications with health related functions routinely share user data with third parties, including for-profit corporate entities, without oversight or transparency.[25] Despite collecting large volumes of personally identifiable and potentially sensitive health information, a number of health apps do not provide even basic privacy assurances or protections.[26] While the

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most sophisticated app-mediated studies are likely to have participant privacy protections in place,[27] the same is not assured in the case of research conducted by nontraditional researchers.

From an international perspective, the consequences of unforeseen or uncontrolled data sharing may be particularly serious. For one thing, unregulated researchers may share, or be compelled to share, collected information with government agencies or other third parties. This risk that foreign entities may have access to a participant's personal health information appears to be heightened when research arrangements cross borders. The risk of this kind of sharing, especially if not contemplated in informed consent documents or disclosed prior to the study, could potentially cause deep harm to participant privacy. Information shared with state agencies, for example, could be used for discriminatory effect in administrative proceedings.

Commercialization

While mobile health research has been given much attention as a promising development in medical science, with the potential to advance knowledge and lead to improved disease treatment and management,[28] it is also part of a more complex, lucrative commercial system. Smartphone applications with health-related functions form a large and growing industry. By some estimates, that industry is worth at least $23 billion.[29] App-mediated studies are being increasingly conducted by researchers outside of the academy, many of whom may have the commercialization of research results as a primary motive of their work. This raises a number of policy questions. Whether and how the potential commercialization of research results is communicated to participants during the informed consent process, for example, is an important ethical consideration.[30] Additionally, the potential for the commercialization of app-mediated research results might raise trust issues in the interactions between researchers and participants. It is well-documented in the biobanking context that participants are generally less trusting of commercial researchers than university-affiliated researchers.[31] As app-mediated research among nontraditional researchers grows, it will be important to find mechanisms that ensure participant trust and robust informed consent.

For app-mediated research conducted internationally, the above policy considerations will be even more pressing. Issues of participant trust, for example, might be exacerbated when research is conducted by a foreign entity.[32] Ensuring transparency in the informed consent process, both about who is conducting the research and how results may be used, will play a critical role in maintaining the delicate trust between researchers and participants. At the same time, there is an emerging consensus among researchers, including those who are university-affiliated, that commercializing study results is the most promising way to bring innovations into public use and may even constitute an ethical responsibility.[33] This suggests that the continued commercialization of research results might be inevitable, underscoring the urgency of accounting for such trends in our assessment of international app-mediated studies.

Research Ethics

Requirements for ethics review are a primary mechanism through which medical research is regulated. International research generally complicates the applicability of such requirements, and this is almost certainly true in the case of app-mediated research as well. It may be unclear where such projects should be submitted for ethics approval, whether research ethics committee decisions would apply across jurisdictions, and whether it is possible to enforce existing rules against non-scientist researchers. Where ethics review is sought at multiple sites, there is a profound risk that the process will be inefficient and costly.[34] Conventional ethics review systems, moreover, will sometimes be at odds with the structure of citizen science projects.[35] These factors suggest that requirements for ethics approval for international app-mediated studies carried out by nontraditional researchers is likely to be complicated and unclear.

Against this backdrop, some have proposed a "safe harbor" framework of ethics equivalency for biomedical research across jurisdictions.[36] On this model, international ethics review may be harmonized according to "globally transposable research ethics norms and principles."[37] This would be facilitated by an international compact and the creation of an agency formed to facilitate ethics review for multisite international studies. While this sort of approach would potentially help address some of the difficulty in managing ethics approval for international app-mediated studies, it is only one approach. As smartphones become more centrally important research tools, it will be necessary to develop clear and consistent approaches to ethics approval.

Conclusion

Each of the issues described above, of course, are likely to be important considerations whether or not app-mediated research is internationally oriented. When such research is extended abroad, however, these issues take on a uniquely challenging connotation. In the following section of this paper, we will describe

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how such challenges may be addressed by certain existing international policy norms. However distinct the issues raised by app-mediated research, the regulatory situation at the international level may be significantly unalike that in the United States. While such research may be unregulated in the United States, insofar as it is properly considered "research," existing international norms are likely applicable, potentially situating such research in an already well-established ethics framework.

Existing Policy Norms and International App-Mediated Research

International normative guidance specifically aimed at app-mediated research is sparse. This is not to say, however, that such research is unregulated. The regulatory lacuna described elsewhere in this symposium derives primarily from the idiosyncratic manner in which medical research is governed in the United States. But the regulation of research in most countries does not depend on a study's source of funding.[38] Instead, the dominant regulatory question is whether an activity constitutes medical research. If it does, it will generally fall into the state's domestic system for regulating research.

Beginning from the view that app-mediated research is not fundamentally ethically distinct from other categories of medical research, existing international policy norms might help to fruitfully guide the execution of app-mediated studies.

For that reason, while app-mediated studies conducted by nontraditional researchers may be systematically unregulated in the United States, the same is unlikely to be true in other countries. It is thus worth stressing that we can expect international app-mediated studies to be governed according to the standard domestic regulatory regimes that would apply to any other kind of medical research. The critical question, then, is not whether a study conducted by a nontraditional researcher is funded by a particular body, but whether it is research. Broadly speaking, app-mediated studies do not appear to be fundamentally ethically distinct from other kinds of medical research. App-mediated studies apply different tools and processes, but ultimately aim at the same set of objectives as conventional research, chief among them the expansion of knowledge and improvement of the human condition.

Of course, there are numerous complications in the regulation of research facilitated by mobile applications. These tools permit researchers to recruit from large sections of the population, to passively collect massive amounts of personal health information, and to potentially follow up with participants on a frequent and ongoing basis. These features raise novel policy challenges, many of which may need to be contemplated in standalone guidance. Domestically, strategic plans and guidance documents for mobile health and electronic health have been issued by agencies in a diverse number of countries. Some examples include South Africa,[39] France,[40] and Singapore.[41] In all, just over 120 countries have national strategies for mobile or electronic health, many of which contemplate mobile health applications directly.[42]

Notably, however, such strategies do not usually engage with the policy implications of conducting research with mobile health tools and the regulatory landscape at the level of individual countries is, at present, poorly developed. There may be two reasons for this. First, much of the mobile health research focus thus far has been in the United States. As we described above, for example, most of the app-mediated studies presently available on the largest app stores are only available to download in the United States. Second, given that app-mediated research is likely to be subsumed in domestic research regulation, it is possible that regulators have not yet felt directed pressure to address policy concerns in this space.

Likewise, at the supranational level, regulatory coordination on the issue of mobile health application use and development is nearly nonexistent.[43] While certain scholars have proposed the development of a global framework for assessing mobile health apps,[44] there is no indication that the realization of such a framework is forthcoming. On the more precise issue of app-mediated research, international regulatory tools have not yet provided much in the way of explicit guidance. But the absence of explicit guidance does not suggest that there is no applicable international regulation whatsoever. Beginning from the view that app-mediated research is not fundamentally ethically distinct from other categories of medical research, existing international policy norms might help to fruitfully guide the execution of app-mediated studies.

In what follows, we will consider international policy norms applicable to app-mediated research, even if they do not contemplate such research explicitly.

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We will briefly explicate how such guidance might be interpreted in light of ongoing shifts in medical research practices. Of course, the regulatory instruments we discuss in this section do not constitute an exhaustive list of measures that may be applicable in this context. Among international research norms there is significant overlap in the ways they approach the issues in question. We will focus primarily on approaches to the ethical concerns identified in the above sections of the paper.

Informed Consent

The informed consent implications of app-mediated research are likely to be modulated by several international policy documents. The World Medical Association's Helsinki Declaration, for example, is perhaps the most influential international research ethics document.[45] While it does not explicitly contemplate app-mediated research and is primarily addressed to physicians, its broad statement of research ethics principles may be a helpful guide for nontraditional researchers conducting app-mediated studies as well. In recent years, some have argued that citizen scientists could help to promote the public trust and increase the credibility of their work by adhering to the participant protection standards detailed in the Helsinki Declaration.[46] The Declaration sets out specific requirements for securing informed consent, including that prospective participants are "informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study."[47]

These informed consent requirements, of course, are not uniquely present in the Helsinki Declaration. The CIOMS Guidelines likewise maintain that researchers have an obligation to obtain the informed consent of prospective participants.[48] Notably, the Council for International Organizations of Medical Sciences (CIOMS) stresses that informed consent should only be obtained after all necessary information about the research project has been communicated. Unaffiliated or otherwise nontraditional researchers should clearly disclose their status as citizen or commercial scientists in the informed consent process. Sources of funding should similarly be clearly disclosed during recruitment in order to avoid real or perceived conflicts of interest.

Privacy

The privacy implications of mobile health are pervasive. The United Nations Special Rapporteur on the Right to Privacy's Task Force on Privacy and the Protection of Health Data has specifically addressed such issues in draft recommendations on the protection of health data. These draft recommendations clarify that the "the same legal protection and confidentiality applicable to other health-related data processing."[49] The recommendations stress that individuals who use mobile apps for health data processing must have the privacy implications of such use explained to them prior to engaging with the application.[50] The Helsinki Declaration, notably, stresses the importance of protecting the "life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects."[51] Article 24 of the Declaration specifies that "every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information."[52] In light of the particular risks associated with app-mediated research, as we outlined above, the protection of the privacy interests of participants should be a central consideration in the design of app-mediated studies.

Like the World Medical Association, the Organization for Economic Cooperation and Development (OECD) has taken a recent interest in the growth of mobile health technologies. In October 2016, it issued the results of an expert consultation on mobile health held as part of the OECD-Harvard Global Health Institute Workshop.[53] This document contemplates health research directly on several points. In particular, the OECD identifies the central importance of maintaining relationships of trust among stakeholders, including in the provision of health services and the conduct of health research. In this regard, ensuring privacy is intimately related to maintaining the public's trust.[54]

Commercialization

The issue of commercialization in international policy norms is often framed explicitly in terms of informed consent. The CIOMS Guidelines, for example, specify in Guideline 1 that the commercial intentions of health researchers should be disclosed in the course of securing participant informed consent.[55] Importantly, article 12 of the Helsinki Declaration specifies that "medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications."[56] The CIOMS in its International Ethical Guidelines for Health-related Research Involving Humans takes a similar position.

In Guideline 1, for example, the CIOMS Guidelines describe the importance of having properly trained scientific personnel and of communicating the qualifications of researchers to prospective participants during the informed consent process.[57] This may serve to restrict the class of citizen scientists capable of conducting research that complies with international eth-

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ics norms. For private entities conducting app-mediated research for primarily commercial purposes, it may be difficult to assess researcher qualifications. While institutional affiliation may provide some measure of assurance of researcher qualification when the institution in question is a university, the same does not appear to be true in the case of less traditional research entities. The OECD, likewise, points to the importance of transparency and accountability in health research.[58] For app-mediated studies, the overriding ethical consideration on the issue of commercialization may be that participants are adequately informed about what will happen to the fruits of the study in question.

Research Ethics

The Helsinki Declaration takes a fairly strict approach to ethics review. Article 23, for example, requires that research protocols involving human subjects "must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins" and that the committee have "the right to monitor ongoing studies."[59] The reviewing committee must be transparent, independent, and must not be influenced by the researcher or the researcher's institution. The CIOMS Guidelines go somewhat further, describing requirements for the formation of an ethics committee. The Guidelines state clearly that "all proposals to conduct health-related research involving humans must be submitted to a research ethics committee to determine whether they qualify for ethical review and to assess their ethical acceptability."[60] In the case of international research, the Guidelines require coordination between ethics committees in different countries. Such committees "should establish efficient communication" mechanisms for the coordination of research ethics review.[61]

Despite the clarity of such guidelines, questions remain about the obligations of nontraditional researchers to obtain research ethics approval. A citizen researcher might not know to which research ethics committee their project is best submitted. On this measure, industry self-regulation might be determinative, at least on the question of whether ethics review is required. Persons using the ResearchKit platform to develop app-mediated studies, for example, are required to obtain research ethics approval before posting their study, irrespective of whether there is a regulatory obligation to do so.[62]

Conclusion

Expanding on the themes above, the World Medical Association also issued a statement on mobile health in 2015.[63] While the Statement does not explicitly contemplate mobile health research, its recommendations on the clinical use of smartphone applications might be contextually important in app-mediated protocol design. For example, the Statement urges smartphone apps to be primarily used "to eliminate deficiencies in the provision of care or to improve the quality of care."[64] Analogized to the research context, mobile health research might be best applied where it serves to address gaps in conventional medical research. The Statement similarly calls on the medical community to develop "standards and certification schemes" to ensure the "interoperability, reliability, functionality and safety of mHealth technologies."[65] Clear safety standards for mobile health would help to facilitate the design of research apps that protect participant privacy and safeguard them from the erroneous or misleading health information that may be provided by such applications.[66] In this vein, however, the European Commission has pointed to the difficulty of developing policy guidelines specifically aimed at mobile health research. Building consensus on this issue has proven to be "a much more complex exercise than expected."[67]

The development of reliable, explicit international policies for the management of app-mediated research is thus likely to be challenging. For the moment, then, it may be necessary for nontraditional researchers to draw on existing international tools and frameworks for organizing their work. One possible alternative avenue that might deserve further consideration intersects with the DIY Bio movement, an informal community of non-scientist biologists running scientific experiments in nontraditional research settings.[68] The DIY Bio movement shares a clear resemblance to trends in app-mediated research, especially in light of the increasing prevalence of citizen scientists operating in that space. As part of the DIY Bio movement, open source codes of ethics have been made available online for non-scientist researchers to consult and modify as they wish.[69] While not international normative guidance in any conventional sense, this sort of approach applied in the context of international unregulated app-mediated research might help provide further structure in emerging research trends. Just as mobile health technologies are increasingly making health research tools broadly available, so too might open source ethics frameworks make the difficult work of regulating these novel studies a more collaborative, citizen-centered practice.

Conclusion

In this paper, we have sought to describe the emerging trend of "unregulated" app-mediated medical research from an international perspective. We have

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sketched the contours of such research, contemplated the particular policy challenges it is likely to face, and proposed the view that existing international policy frameworks may provide a degree of ethics guidance. For research subject to regulation in one country and subsequently extended to another, the standard course of ethics review and oversight for medical research should apply. In the case of citizen science or research otherwise not subject to regulation in a home jurisdiction, standard research ethics principles, such as those contemplated in the Helsinki Declaration and elsewhere, should be considered in the course of study design. Less traditionally, non-scientist researchers pursuing app-mediated studies may find guidance in open source ethics codes, such as those developed by the DIY Bio movement and made accessible online for adoption or revision.

In years to come, it will be important for scholars and policymakers to carefully consider the ethical and legal dimensions of emerging app-enabled research paradigms. At the same time, it is worth remembering that app-mediated studies, while they vastly complicate some of our conventional assumptions about medical research, should fundamentally be assessed and regulated according to the principles and structures that have historically applied to conventional health research. In that way, while app-mediated research signifies an important transition in medicine, it does not signify a departure from the ethical and legal principles that govern it.

Note

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