**ADDRESSING ELSI ISSUES IN UNREGULATED HEALTH RESEARCH USING MOBILE DEVICES**

**RESEARCH PLAN**

**A. SIGNIFICANCE**

In the last decade there has been explosive growth in the collection of individual health data on mobile devices. According to the Food and Drug Administration (FDA), in 2015, there were about 500 million smartphone users worldwide using one or more health apps, with the number expected to grow to 1.7 billion by 2018.[[1]](#endnote-2) Also, in 2015, there were 90,000 health apps available on iTunes and 75,000 health apps available from the Android app store.[[2]](#endnote-3)

Mobile health apps have become increasingly sophisticated. The numerous apps fall into two general categories: (1) those that utilize existing hardware on the phone or other device (e.g., cameras, accelerometers), and (2) those that utilize external hardware, including wearables. External hardware can convert smartphones into electronic stethoscopes, ultrasound machines, blood test platforms, and other advanced medical devices.[[3]](#endnote-4) Thus, mobile devices are not merely fancy telephones or portable entertainment systems; they are powerful hand-held computers that can be configured with hardware and software into a staggering array of health-related electronic wizardry.

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| Figure 1. 1.F | | | |
|  | Research covered by Common Rule | Research NOT covered by Common Rule |  |
| Data gathered for research | Use of mHealth by traditional researchers | Independent research  Patient-enabled research  Citizen science |  |
| Data NOT gathered for research | Research use of health app data collected for a clinical purpose | Research use of health app data collected for another purpose |  |
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Because of the ubiquity of mobile devices, the popularity of health apps, the range of collectible health information, and the interactive capacity of the Internet, it was inevitable that mobile devices would begin playing an increasingly important role in health research. The ethical, legal, and social issues raised by research using mobile devices depend on two distinguishing characteristics: (1) whether the health information was originally collected for research, and (2) whether the research is subject to the Federal Policy for Protection of Human Subjects (Common Rule) (Figure 1). Research using mobile devices subject to the Common Rule is conceptually quite similar to other traditional health research because it involves the collection, analysis, storage, and transmittal of health information to professional researchers at regulated institutions. This research, although certainly important, is not the subject of this grant application.

Instead, we propose to study the ELSI issues in unregulated health research using mobile devices. The lack of legal regulation or self-regulation by app developers and other entities creates a significant risk of harm to research participants and the public in four broad categories: (1) physical harms can result when apps used in research provide erroneous health information that participants rely on to their detriment, such as foregoing essential treatment or taking ineffective or harmful medications and supplements; (2) dignitary and psychological harms could result from inadequate privacy protections that lead to the disclosure or sale of sensitive information, or psychological harm caused by erroneous assessments of health risk; (3) economic harms could result from medical identity theft and other harms caused by inadequate data security; and (4) societal harms could result when improperly performed research leads to flawed scientific conclusions relied on by numerous individuals. Notwithstanding these risks and the tremendous growth of health apps, the ELSI implications have not received much attention from health researchers, mobile device and app developers, scholars, patient advocates, regulators, and policy makers.

As shown on the right side of Figure 1, unregulated research may be divided into (a) research involving data specifically gathered for research, but carried out by nontraditional researchers (such as independent organizations not subject to the Common Rule, patient groups, and "citizen scientists"); and (b) data collected by health apps for other purposes and converted to a research use. We propose the following interrelated aims: (1) We will conduct in-depth, qualitative interviews of thought leaders from key stakeholder groups; (2) A Working Group of 24 experts utilizing results of the thought leader interviews will conduct an in-depth analysis of the regulatory framework for research with human subjects and the underlying ethical principles embodied in current research regulations that ought to be a part of voluntary guidelines or regulatory standards; and (3) We will disseminate information and recommendations to app developers, key stakeholder groups, and policy makers.

**Attributes of unregulated health research using mobile devices; preliminary studies.**

The first three types of unregulated research discussed below – independent research, patient-enabled research, and citizen science research – often overlap, and it is likely that new forms of research will evolve over time. Although only independent researchers have so far utilized mobile devices to any great extent, it is inevitable that patient-enabled and citizen science research will also make use of this technology.

1. *Independent research*. To take advantage of new software supporting health research on mobile devices, in 2015, the first major smartphone-based health research study was conducted by Sage Bionetworks, an independent, nonprofit research organization based in Seattle. The Parkinson's disease mPower study combined the Apple ResearchKit mobile health application platform with additional software developed by Sage Bionetworks. Participants were recruited online in partnership with collaborating Parkinson's disease organizations. The study utilized a novel, highly visual, self-guided consent process. Study data were generated by recording the voices of the participants, their posture and stability, their reaction time, and other measures of Parkinson's disease symptoms. Approximately 17,000 participants enrolled in the study over a six-month period.

The mPower study was notable because it used online informed consent and external review in accordance with prevailing research ethics to guide participation, data collection, and use. Nevertheless, because the research was neither federally funded nor otherwise subject to federal research regulations, there was no legal mandate to do so. The groundbreaking online consent process and other ethical aspects of the research were under the direction of John T. Wilbanks of Sage Bionetworks, who is a multiple-PD/PI on this grant application. The external research review was conducted by WIRB-Copernicus Group IRB. David G. Forster, Chief Compliance Officer of WIRB-Copernicus Group, will be a speaker at Working Group Meeting #2.

In 2016, two key personnel on this application from Sage Bionetworks, John T. Wilbanks (PD/PI) and Megan Doerr (co-investigator), undertook a qualitative analysis of mPower research participant perspectives. The app for this study provides users with a text field to collect open-ended comments and feedback. Of 7,500 comments, 3,888 involved user perspectives on ELSI issues, such as consent, data sharing, and governance. Analysis of these comments provides a number of insights relevant to this grant application. For example, many participant comments indicated an interest in research participation as citizen scientists, offered opinions on promising research uses of the data already collected, suggested how to analyze data, and recommended other Parkinson’s symptoms to study.

Although Sage Bionetworks was the first research entity to enter this space, new research apps are being introduced for both ResearchKit (Apple) and ResearchStack (Android). Other mobile device-based, independent research includes the Microbiome Study (U Biome); Biogram 2 -- Biometric Measures (Medable, Inc.); and COPD Navigator (LifeMap Solutions).[[4]](#endnote-5)

2. *Patient-enabled research*. Patients and their family members long have been involved in financing and lobbying for increased health research. In recent years, the growth of information technology has facilitated a variety of ways for patients to participate more closely in research. One way is through the sharing of health records, biospecimens, and patient registries that support research and enable participation in research. An example of such a program is the Bio Trust program of the Genetic Alliance, a large organization that serves as a clearinghouse of information and source of activism for numerous genetic diseases. The motto of this research effort is: "We will beat a path to participation in biomedical research, and we will accelerate solutions." Sharon F. Terry, President and CEO of the Genetic Alliance, is a member of the Working Group.

Another example of patient-enabled research is Crohnology. Focusing on Crohn's disease, it is a self-described "patient-powered research network," which serves as a common resource allowing patients to contribute their treatment outcomes to support aggregate compilations for research. Sean Ahrens, Founder of Crohnology, is a member of the Working Group.

In some cases, patients actually initiate and direct the research. For example, after the publication of a small Italian pilot study of patients with amyotrophic lateral sclerosis (ALS),[[5]](#endnote-6) patients on the forum of PatientsLikeMe decided to test the theory for themselves. Over the course of 2 years, 149 patients obtained lithium off-label and, using the ALS functional rating scale, tracked their progress. A published study, conducted internally at PatientsLikeMe, concluded that lithium had no effect on disease progression."[[6]](#endnote-7) The patient-initiated null finding undoubtedly prevented many patients from undertaking this ineffective and potentially risky therapy. Sally Okun, Vice President for Advocacy, Policy, and Patient Safety of PatientsLikeMe, will be a speaker at Working Group Meeting #1.

3. *Citizen science*. The term citizen science can include a variety of arrangements where nonscientists assist in or contribute to research, including data capture and crowdsourcing.[[7]](#endnote-8) The most extreme form of citizen science, and the one that raises the most ethical issues, involves amateur scientists independently undertaking scientific studies. Some of the research is purely informational and involves "big data" analytics applied to health information. Other research involves direct acquisition and analysis of clinical measures. DIY Genomics and Quantified Self are two groups noteworthy for their efforts in this field. Ernesto Ramirez, Program Director of Quantified Self, will be a speaker at Working Group Meeting #1.

A study of the rs1801133 allele of the MTHFR gene was designed to demonstrate the feasibility of citizen science research.[[8]](#endnote-9) Using direct-to-consumer genetic tests, the study attempted to correlate the presence of the allele with homocysteine response to vitamin B supplements of active and inactive forms, which were measured through analyzing the blood of the participants. The study demonstrated that the effectiveness of certain interventions to lower homocysteine levels varied with the presence of particular alleles and, more generally, that successful citizen science studies on genomics are possible.

4. *Data not gathered for research*. Health apps, including wearables, typically collect significant amounts of individual health data. In addition, many apps collect other information about and unbeknownst to the user, including user location, messages, “photos, videos, credit card information, and even facial features.”[[9]](#endnote-10) Permission to activate the camera, microphone, or tracking on a phone may be required in order to download an app.[[10]](#endnote-11) Although some apps have privacy policies, “it is nearly impossible for users to maintain control of their data, its diffusion, and subsequent uses . . . [and therefore] the notion of consenting to research use of data loses meaning.”[[11]](#endnote-12)

The volume and value of data from mobile devices has soared, and it has spawned an entire industry of data brokers. Data collected from apps generated “an estimated $5.5 billion in revenue in 2013.[[12]](#endnote-13) Most of the revenue is generated through marketing, but an unknown and undoubtedly growing amount of revenue is derived from research.” Among the many customers of health data brokers are pharmaceutical companies.[[13]](#endnote-14) There have been no detailed studies of the unconsented research uses of health app data, but in light of the amount, nature, and value of the data; the ease with which it can be monetized; and the lack of regulation; it would seem that the sale of health app data to researchers is taking place now and will become increasingly common. Indeed, preliminary studies have documented the sharing of health information obtained by mobile apps,[[14]](#endnote-15) including selling information for research.[[15]](#endnote-16)

**Regulation of research and mobile devices.** The first step in analyzing the ELSI issues raised by health research using mobile devices is to determine whether the Common Rule or other regulations apply.

1. *Applicability of the Common Rule.* The Common Rule applies "to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make the policy applicable to such research."[[16]](#endnote-17) In addition, the Common Rule applies to all research, regardless of funding source, undertaken by entities that have signed a Federal-wide Assurance with the Department of Health and Human Services.[[17]](#endnote-18) Virtually all American academic and health care institutions are subject to the Common Rule for all of their research involving human participants. Other research directed or funded by any of the 18 Common Rule signatory agencies is also covered. Research undertaken and funded by independent entities or individuals, however, is generally not subject to the Common Rule.

2. *FDA regulation of research.* The FDA has issued its own regulations that generally mirror the Common Rule.[[18]](#endnote-19) They apply to research involving investigational drugs and medical devices using human participants.[[19]](#endnote-20) Any research intended to support a submission to the FDA for approval of a drug or medical device must comply with the FDA regulations. The FDA regulations apply to privately-funded research using human subjects undertaken by pharmaceutical and medical device companies and their research partners, but research not undertaken to support an application to the FDA is not subject to these regulations.

3. *FDA regulation of mobile health (mHealth) applications.* Despite the inapplicability of its research regulations to certain classes of mobile health research, the FDA still has an important role in research with mobile devices. The FDA has announced that it will regulate "mobile medical applications" by applying the same "risk-based approach" it uses to "assure the safety and effectiveness for all medical devices."[[20]](#endnote-21) The FDA plans to regulate apps intended to be used as an accessory to a regulated medical device or that transform a mobile platform into a regulated medical device."[[21]](#endnote-22)The FDA will not regulate apps that provide patients with simple tools to organize and track their health information, give patients easy access to information related to health conditions or treatments, or help patients communicate with their health care providers.[[22]](#endnote-23) Also excluded from coverage are apps that allow a user to collect and track heart rate, weight, and similar biometric information.[[23]](#endnote-24)

There is a clear need to regulate mobile health apps because many app developers "do not have medical training and often do not involve medical experts in the design process."[[24]](#endnote-25) The result is a risk to patient safety, which could also extend to research participants if the apps are used for research. For example, in a study of 46 smartphone apps for calculating insulin dose based on planned carbohydrate intake, 67% of the apps provided inappropriate dose recommendations.[[25]](#endnote-26) Another analysis of 77 cancer apps available in the Apple App Store found that only 55.8% of the apps dispensed clinically validated data.[[26]](#endnote-27)

4. *FTC regulation of mobile health (mHealth) applications.* The Federal Trade Commission (FTC) enforces the FTC Act, which prohibits deceptive or unfair acts or practices in or affecting commerce, including those related to privacy and data security, and those involving false or misleading claims about the safety or performance of an app. The FTC also has issued the Health Breach Notification Rule, which requires certain businesses to notify the public following breaches of personal health information. The FTC, along with the FDA, the Office of the National Coordinator for Health Information Technology, and the Office for Civil Rights of the Department of Health and Human Services (HHS), has issued a joint interactive tool to provide guidance for the regulations applicable to mobile health apps.[[27]](#endnote-28)

5. *HIPAA Privacy Rule and research.* The main regulatory basis for protecting the privacy of participants in health research is the HIPAA Privacy Rule,[[28]](#endnote-29) which applies to three classes of covered entities (health providers, health plans, and health clearinghouses) and their business associates (an individual or entity that assists covered entities with functions such as claims processing, utilization review, quality assurance, legal services, management, and financial services).[[29]](#endnote-30) Research undertaken by a HIPAA covered entity, such as an academic medical center, is subject to the Privacy Rule. Intramural research undertaken by a pharmaceutical company, however, would not be subject to the Privacy Rule. The Privacy Rule requires that any research uses and disclosures of individually identifiable health information must have a written authorization signed by the individual.[[30]](#endnote-31) There have been increased efforts at the Congressional and regulatory levels to relieve the perceived burden on researchers created by the Privacy Rule, and mHealth research adds another dimension to the ongoing policy debate about the conflict between individual privacy interests and the public good of open access to health information.

**Traditional elements of research ethics.** In the absence of federal regulatory coverage for certain health research using mobile devices, the key question is what, if any, type of regulation is necessary or desirable to safeguard the welfare of research participants. In extending some level of research ethics guidance to previously unregulated mHealth research it may be necessary to develop an entirely new paradigm for research ethics. In other words, the traditional bimodal structure of research regulation (i.e., extensive regulation vs. no regulation) may be disrupted by new technologies creating hybrid categories of informational and even interventional research. The regulatory treatment of health research with mobile devices is likely to force this reconceptualization. The first attempt to explore these issues was a 2015 article by Rothstein, Wilbanks, and Brothers,[[31]](#endnote-32) all of whom are key personnel on this grant application.

1. *Oversight by IRBs and other types of research governance*.The requirement for IRB review reflects a longstanding principle that research should be subject to oversight by an independent ethics panel to protect the welfare of the participants.[[32]](#endnote-33)This, arguably paternalistic, approach has been implicitly rejected by some new models of research, such as patient-directed research, which emphasize the ability of research participants to interact with investigators as equals in the research process. Thus, many citizen science investigators would be reluctant to submit to IRB oversight voluntarily because of concerns that it would be a barrier to efficient and nimble research. Accordingly, in our Aim 1 interviews we will examine how citizen scientists and other researchers perceive the burdens and benefits of external ethics review. In Aim 2, the Working Group will consider policies that exclude non-federally funded research from oversight and whether certain key elements of IRB oversight may be adapted to form a hybrid, streamlined type of oversight for voluntary adoption by unregulated researchers.

Several possible models of research governance have been adopted by international consortia of researchers. These organizations have developed detailed guidance on many aspects of research protocol development, recruitment, consent, data collection, storage, access controls, data sharing, and other matters. The Global Alliance for Genomics and Health, a group containing over 400 organizational members from 69 countries,[[33]](#endnote-34) is a leader in this field. Bartha Maria Knoppers, a member of the Steering Committee of the Global Alliance, is a member of the Working Group.

2. *Recruitment and inducements for participation.* Coercive practices and financial inducements in mHealth research could threaten participant autonomy.[[34]](#endnote-35) One concern is whether recruitment for patient-directed research, especially by individuals with the same illness, is coercive in a way that traditional recruitment is not. Although participants in mHealth research may be motivated to participate by the offer of access to research data, including their own records, there is still a significant risk that a participant's decision to enroll in research will be motivated by the therapeutic misconception as to possible benefits to their own health or misapprehending the likelihood of near-term scientific discoveries that could benefit others.[[35]](#endnote-36) In Aim 2, the Working Group will study the recruitment process for research using mobile devices.

3. *Inclusion, exclusion, and the input/output problem.* Increasing participation in health research among populations that have long been underrepresented is an important goal because health research disproportionately helps individuals whose ancestry and social environments are similar to the research participants.[[36]](#endnote-37) This has been referred to by S. Malia Fullerton (a member of the Working Group) as the "input/output problem."[[37]](#endnote-38) Mobile devices may prove to be an important tool for achieving greater diversity among participants in health research because they provide access to the Internet for many members of minority groups and low-income Americans who have no alternative.[[38]](#endnote-39) It remains unclear, however, whether access to mobile devices will translate into increased research participation and biological diversity. Finally, an online participant might fraudulently misrepresent his or her eligibility, misstate key facts, or participate multiple times.[[39]](#endnote-40) In Aim 2, the Working Group will address these important issues.

4. *Informed consent.* Informed consent, the touchstone of modern research ethics, contains two important elements: (1) the obligation of researchers to inform potential participants about known risks and benefits, as well as other relevant information; and (2) the autonomy of individuals to decide whether to participate, with additional protections for individuals with diminished autonomy (e.g., children and adults with intellectual impairments). Research with mobile devices challenges traditional notions of informed consent in that, historically, informed consent has been in the context of face-to-face interactions by investigators with potential research participants. Translating informed consent to online research has been difficult.[[40]](#endnote-41) A highly interactive online consent process was developed and successfully used by John Wilbanks of Sage Bionetworks, PD/PI on this grant application. Nevertheless this model of informed consent has not been widely adopted. We will study the necessity and viability of informed consent as well as possible new methods of informed consent for mHealth research.

5. *Confidentiality and security.* Regulated health researchers are legally required to safeguard the health information of research participants in accordance with the research protocol, only disclosing health information according to the informed consent document or when compelled by law.[[41]](#endnote-42) In Aim 2, the Working Group will consider if a traditional or modified confidentiality obligation should apply to unregulated mHealth researchers and whether assurances of confidentiality made by these researchers can be enforced or breaches redressed. We also will analyze whether strategies can be designed to prevent information from non-participants from being inadvertently captured by mHealth researchers. Finally, the issue of security is implicated when health information, including clinical records, is transmitted electronically. We will study whether the same standards for security, including encryption and participant identity verification, should apply to unregulated mHealth research.

6. *Children and other vulnerable participants.* Vulnerable research participants, including children and intellectually impaired adults, raise difficult issues for mHealth research.[[42]](#endnote-43) In face-to-face research, investigators are able to evaluate the competence of the individuals to consent or assent to research participation and, when necessary, to identify the competent adult legally authorized to give permission in their stead. In addition, putting demographic and health information about children on unsecure mobile devices and transmitting it electronically could create a risk that it would be intercepted by persons intending harm, such as pedophiles or estranged parents. In Aim 2, the Working Group will consider the unique issues raised by unregulated mHealth research using vulnerable research participants. Kyle Brothers, an expert on pediatric research ethics, is a co-investigator.

7. *Incidental findings and return of results.* Substantial recent scholarship has been devoted to the issue of whether researchers, especially those engaged in genetic or genomic research, are required, permitted, or prohibited from disclosing incidental findings to research participants.[[43]](#endnote-44) Two leading experts, Ellen Wright Clayton and Susan Wolf, members of the Working Group, will lead the research on this issue. Several factors are frequently mentioned as important, including the strength of the genetic association, the severity of the condition, and the clinical actionability of the finding. It is difficult to imagine that unregulated mHealth research containing few of the characteristics of the researcher-participant relationship would have comparable ethical obligations to disclose incidental findings. Nevertheless, a consent document could be the basis of a duty to disclose some findings and participants in all forms of research may increasingly expect such information. Assuming that the researchers wanted to offer to disclose incidental findings and that the participants wanted to receive them, it is not clear how the sharing of information would or ought to proceed in the absence of an in-person relationship. In Aim 2, the Working Group will study the challenges surrounding incidental findings and the return of results.

8. *Publication and data sharing.* Researchers contemplating disclosing the results of health research may be influenced by two countervailing pressures. One pressure is the interest in being the first to announce the discovery of a particular finding (sometimes derided as "publication by press conference"). The opposite pressure is to suppress findings (sometimes criticized as "hoarding"), which may be based on intellectual property considerations or the interest in being the sole researcher able to conduct follow-up studies. Although the NIH has adopted detailed regulations requiring NIH-funded researchers to provide public access to data and publications,[[44]](#endnote-45) these rules do not apply to unregulated researchers.[[45]](#endnote-46) In Aim 2, the Working Group will study publication and data sharing by unregulated researchers using mobile devices and whether scientific journals should publish the findings of unregulated research.

**B. INNOVATION**

The proposed research is highly innovative. A comprehensive analysis of the ELSI issues raised by unregulated mHealth research is timely, important, and unprecedented. It is closely related to the Precision Medicine Initiative (PMI) and other research activities of the NIH. Indeed, one of the "use cases" of the PMI is "use of mobile (mHealth) technologies to correlate activity, physiologic measures and environmental exposures with health outcomes …."[[46]](#endnote-47) Each of the proposal's 3 aims consists of unique and innovative elements. Aim 1 includes the first detailed interview study of thought leaders in mHealth research, including citizen scientists, independent researchers, patient-directed researchers, health app developers, patient advocates, IRB officials, and policy makers. Findings and insights from these interviews will help guide Aim 2, in which a Working Group of leading scholars and other experts in diverse fields, including bioethics, law, medicine, biological and social sciences, and research oversight, will be joined by patient advocates, technology developers, and health policy experts. The use of such a diverse group for structured consensus-development is highly innovative. The Working Group will meet 4 times as part of the overall research and consensus-development process. The goal is, if possible, to reach consensus on a range of fundamental issues and, where appropriate, to identify and articulate minority positions. Aim 3 consists of educational programs and translation of the study's analyses and recommendations. Because of the central role of app developers, we will conduct 2 in-person research ethics training sessions for app developers; we will also capture these sessions on videos that will be posted on the Internet. We believe this will be the first time research ethics education has focused on app developers. Another innovative element of Aim 3 is a policy briefing and conference for key stakeholders and public officials, also including the creation of online videos. These distinctive research activities make this proposal innovative and important from both a conceptual and practical standpoint.

**C. APPROACH**

The proposed study combines a variety of research methodologies to conduct an in-depth assessment of the issues and implications of unregulated mHealth research.

**Aim 1: Conduct in-depth qualitative interviews to elicit thought leaders’ perspectives on risks and appropriate protections for participants in unregulated mHealth research.**

The objective of Aim 1 is to elicit thought leader views on the protection of human subjects in the rapidly evolving environment of mHealth research. To attain this objective, we will conduct in-depth interviews with prominent individuals from key stakeholder groups to gather their input on topics such as risks and benefits in mHealth research, and appropriate protections in unregulated situations. The results of Aim 1 will be the subject of at least one manuscript, will provide expert evidence for our Aim 2 analyses and consensus process, and will directly inform our Aim 3 educational and translational efforts.

1. *Sample and sample size justification*: Using purposive sampling, we will conduct up to 50 interviews with individuals in four key stakeholder groups at the forefront of mHealth research: (1) app and device developers; (2) researchers who are integrating mHealth technologies into their studies (including independent and citizen scientist researchers); (3) patient and research participant advocates; and (4) regulatory/policy professionals. Empirical evidence suggests that a minimum of 8-12 interviews per group are needed to reach saturation (the point at which no new information or themes are observed in the data.)[[47]](#endnote-48) We will identify a starting sample within each group based on prominent position within relevant national organizations and entities, as well as authorship on high impact publications on relevant topics. We will expand our sample with suggestions from Working Group members during Working Group Meeting #1, and by referral sampling, i.e., asking participants to suggest others who should be invited for an interview. Professional role and stature are the selection criteria for this Aim. Within this frame, we will make every effort to maximize the demographic diversity of our sample, including asking for assistance in this regard from Working Group members and during referral sampling.

2. *Instrument development and content*: We will develop a semi-structured guide, including standard probes, to direct the interviews; the Appendix contains a draft of the guide. The guide will be oriented around a realistic research scenario involving the use of mHealth apps and devices in cancer care. The scenario (see Appendix) is based on actual technologies[[48]](#endnote-49) with questions designed to explore alternate pivotal attributes, such as the characteristics of the investigators and their setting, study design (e.g*.,* observational versus interventional), and the nature of the data collected. The interviews will focus on topics such as perceptions of benefits and risks in mHealth research, current and appropriate approaches to informed consent, and current and appropriate approaches to protecting privacy and confidentiality. In addition to open-ended questions, we will incorporate close-ended and other question formats, such as rating and ranking exercises, to systematically explore key aspects of these topics. We allocated time at the beginning of the project to further develop and finalize the interview guide, including robust pilot testing to ensure that the questions are understood as intended and address essential issues. At Working Group Meeting #1, we will present the guide and the results of pilot testing to obtain any final feedback.

3. *Procedures*: We will send an email invitation to thought leaders describing the goals of our overall study, along with an information sheet about the interview. Among individuals who indicate willingness to participate, we will schedule a time for a telephone interview at their convenience, and send a copy of the research scenario to review in advance. Under the supervision of Dr. Laura Beskow (co-investigator), highly trained and experienced members of her research staff will conduct the interviews. At the beginning of each interview, we will review the information sheet and ask for the participant’s verbal consent. We anticipate each interview will last approximately 45-60 minutes, and we will offer $100 compensation for participants’ time. With participants’ permission, interviews will be audio-recorded and transcribed.

4. *Data analysis*: The Duke team will lead codebook development, and the coding, analysis, and interpretation of the data. We will upload transcribed interviews into qualitative research software, NVivo 11, and develop a codebook via a standardized iterative process.[[49]](#endnote-50) Specifically, we will first assign structural codes throughout each transcript to delineate each question and response based on our interview guide. Next we will create thematic codes based on the substantive content of the transcripts. Together, the research team will review four transcripts, drawn from the different stakeholder groups, to discuss and develop an initial set of codes. These will be compiled in a codebook that contains the code name, definition, details concerning when to use and not use the code, and example text to which the code has been applied.49 Two team members will independently apply these codes to the transcripts and then compare inter-coder agreement using Holsti’s method.[[50]](#endnote-51) Any discrepancies will be resolved in consultation with Dr. Beskow and the other investigators. This process will be repeated with remaining transcripts, including periodic checks of inter-coder agreement, revisions to the codebook, and recoding of the transcripts as needed to capture any additions or refinements.

Once all data are coded, we will use an applied thematic analysis approach to explore the range of responses within and across stakeholder groups.[[51]](#endnote-52) Research staff will compile a summary report for each structural (question-based) code as a first level analysis of notable themes related to each question. Subsequent analyses will include running queries, generating code reports, and the development of code summary tables and memos, incorporating both structural and content-based (cross-cutting) codes to explore the range of thematic responses within and across stakeholder groups.51

5. *Expected outcomes and dissemination*: The results of this Aim will provide a comprehensive view of thought-leader perspectives at a time of major paradigm shifts in approaches to mobile data collection for health-related research. Our findings will be disseminated in at least one manuscript (and likely more, based on the expected density of the data), as well as at professional conferences. These data will also provide expert evidence for our Aim 2 analyses and consensus process; specifically:

* Preliminary results will be presented at Working Group Meeting #2
* Final results will be presented at Working Group Meeting #3
* Final results will be part of the evidence base considered during the Working Group Meeting #4 consensus process

In addition, the results will be presented at the Aim 3 policy conference, and will inform the content of app developer workshops and educational videos.

6. *Potential problems and alternative strategies*: We do not anticipate problems achieving this Aim. Dr. Beskow has a demonstrated track record in conducting similar interviews on a range of ethics- and policy-related topics (see Biosketch). The primary challenge will be recruiting busy thought leaders for interviews; however, we will draw upon techniques used with success in previous studies, as well as leverage our relationships within the field to identify appropriate candidates and solicit participation. Finally, our timeline anticipates completing most if not all of the interviews between Working Group Meeting #1 and #2, but allows for any remaining interviews to be conducted and incorporated into the final analysis for presentation at Working Group Meeting #3.

**Aim 2: Develop a detailed analysis of the ELSI issues in unregulated health research using mobile devices, including use of a consensus-building methodology.**

The objective of Aim 2 is to facilitate expert analyses of the ELSI issues in unregulated mHealth research, and to reach consensus (whenever possible) on the appropriate approaches to these issues. To attain this objective, we have engaged a diverse Working Group, including technology experts, patient advocates, citizen scientists, physicians, bioethicists, legal academics, human subjects protections professionals, and social scientists. All individuals identified by name on the meeting schedules below are confirmed (see Letters of Support).

The Working Group will be convened in a series of three meetings involving expert presentations and moderated discussion, including our Aim 1 interview plans and results. These meetings, outlined in detail below, will last 1-1.5 days and will be scheduled in cities with convenient airline connections and good meeting facilities. Some will include special guest speakers to help educate Working Group members on key topics. Overall, we will take many steps to ensure that all meetings are structured, efficient, and productive, including: (1) establishing clear goals in advance of each meeting; (2) providing specific guidance to speakers about the issues and questions to be addressed in their presentations; (3) asking all speakers to prepare a brief document summarizing the most important points to consider and policy questions surrounding their topic; (4) closely moderating the discussion to focus on attaining the meeting goals; (5) capturing the discussion via a dedicated rapporteur; (6) synthesizing the presentations and discussion into a summary document after each meeting; and (7) distributing these summaries to Working Group members with emphasis on their relationship to past and future meetings. We will then hold a fourth Working Group meeting at which we will implement consensus development techniques (described below) to address key issues identified through the earlier meetings.

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| **Table 1** − Working Group Roles | | | | |
|  | Attend Workshops 1-4 | Give a presentation | Research and write topic-specific paper | Author on recommendations paper |
| Working Group/Author (n=15) | Yes | Yes | Yes | Yes |
| Working Group/Speaker (n=3) | Yes | Yes | No\* | Yes |
| Working Group/Discussant (n=6) | Yes | No | No\* | Yes |
| \* Although not currently committed to writing a paper, it is anticipated that some Working Group Speakers and Discussants may decide to join as co-authors on other papers or write their own. | | | | |

Working Group members (including key personnel on this grant) may have different roles in this process (Table 1). Most will be undertaking an in-depth analysis of an assigned topic and will present their findings to the Working Group for discussion and debate—which, in turn, will further inform their examination of the topic. They have committed to reporting their final analysis in an article for publication in a symposium issue of the *Journal of Law, Medicine & Ethics*. Other members are not currently planning to write an article (although may decide later to do so), but will be speakers and discussants at Working Group meetings. All Working Group members will be actively involved in identifying the most significant unresolved issues, and will participate in the consensus development process to address these issues. The outcomes of this aim will be a major recommendations paper and symposium issue of *JLME*, and the findings will directly inform our Aim 3 education and translation efforts.

A detailed preliminary schedule for all meetings appears in the Appendix, and summaries of all confirmed speakers and topics for each meeting appear in Table 2. Letters of support for all of these individuals are included with this proposal.

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| **Table 2** −Working Group Discussants | | |
| Name | Title | Affiliation |
| Cynthia Geoghegan | Patient Representative | Patients & Partners LLC |
| Henry T. Greely, J.D. | Deane F. and Kate Edelman Johnson Professor of Law | Stanford University |
| Marc Hurlbert, Ph.D. | Chief Mission Officer | Breast Cancer Research Foundation |
| Eric T. Juengst, Ph.D. | Professor of Social Medicine and Genetics | U. of North Carolina Center for Bioethics |
| Gary E. Marchant, J.D., Ph.D., M.P.P. | Regents' Professor & Lincoln Professor of Emerging Technologies, Law & Ethics | Arizona State University |
| Patricia A. Spears | Co-Vice Chair, Patient Advocate Committee | Alliance for Clinical Trials in Oncology |

**Stage 1: The Landscape.** Working Group Meeting #1, lasting 1.5 days, will focus on establishing a knowledge base about unregulated mHealth research. The purposes of this meeting are: (1) to bring all Working Group members up to speed on the technical aspects of mHealth devices; (2) to explain the software used to link a research app to one of the two main research platforms (ResearchKit and ResearchStack); (3) to explore different forms of unregulated health research, including independent research, patient-directed research, citizen science, and research uses of data obtained for another purpose; and (4) to help shape the direction of the Aim 1 thought leader interviews by providing input on the interview guide and helping identify prospective interviewees. A summary of the topics and speakers follows (see the Appendix for a detailed schedule).

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| **Working Group Meeting #1 -- The Landscape**  San Diego: October 2017 | | | |
| **Topic** | **Speaker** | **Project Role** | **Affiliation** |
| mHealth devices | Eric J. Topol | Guest Speaker | Scripps Research Institute |
| Mobile health research platforms | John Wilbanks (PD/PI) Kevin Patrick | Working Group/Speaker Guest Speaker | Sage Bionetworks U. of California - San Diego |
| Independent research | Megan Doerr (co-I) Steve Hershman | Working Group/Speaker Working Group/Speaker | Sage Bionetworks LifeMap Solutions |
| Patient-directed research | Sharon F. Terry Sally Okun Sean Ahrens | Working Group/Author Working Group/Speaker Guest Speaker | Genetic Alliance patientslikeme Crohnology |
| Citizen science | Nicolas Terry Ernesto Ramirez Steven Keating | Working Group/Author Guest Speaker Guest Speaker | Indiana University Quantified Self Massachusetts Inst. of Tech |
| Secondary use of health app data | Lori Andrews | Working Group/Author | Chicago-Kent College of Law, Illinois Institute of Technology |
| Thought leader interviews | Laura Beskow (co-I) | Working Group/Author | Duke University |

**Stage 2:** Working Group Meeting #2, lasting 1.5 days, will consider the preliminary findings of the thought-leader interviews. The Working Group will discuss how these findings affect their specific areas of research. Additional presentations will consider key principles of health research regulation, with the goal of identifying those elements that might be applied (in some fashion) to unregulated mHealth research. Topics include: (1) Common Rule and proposed revisions; (2) HIPAA Privacy Rule; (3) FDA regulation of research and mHealth apps; (4) role of IRBs and external review of unregulated research; (5) privacy, confidentiality, and security; and (6) data sharing and publication. As the focus shifts to policy development, proposals drafted by the speakers will be presented and discussed. A summary of the topics and speakers follows (see Appendix for a detailed schedule).

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| **Working Group Meeting #2 --Thought-Leader Input and Regulatory Framework** | | | |
| Chicago: March 2018 | | | |
| **Topic** | **Speaker** | **Project Role** | **Affiliation** |
| Common Rule and NPRM | Michelle N. Meyer | Working Group/Author | Icahn Sch. Med. at Mt. Sinai |
| HIPAA Privacy Rule | Mark A. Rothstein | PD / PI | University of Louisville |
| FDA regulation of research | Mary Majumder | Working Group/Author | Baylor College of Medicine |
| FDA reg. of medical apps | Barbara J. Evans | Working Group/Author | University of Houston |
| IRBs and Unregulated Research | Jeffrey R. Botkin Pearl O'Rourke David G. Forster | Working Group/Author Working Group/Speaker Guest Speaker | University of Utah Partners Healthcare WIRB-Copernicus Group IRB |
| Privacy and confidentiality | Amy L. McGuire | Working Group/Author | Baylor College of Medicine |
| Security | Andrea M. Matwyshyn | Working Group/Author | Northeastern U. Sch. of Law |
| Data sharing | Heather L. Harrell | Co-Investigator | University of Louisville |
| Thought-leader interviews | Laura Beskow | Co-Investigator | Duke University |

**Stage 3:** Working Group Meeting #3, lasting one day, will build on the general principles elucidated at the prior meeting and consider additional recommendations for unregulated mHealth research. Issues to be presented and discussed include: (1) governance and oversight models, including guidelines of research consortia; (2) models of online consent; (3) diversity of research participants and special challenges of vulnerable individuals; and (4) policies for return of results and incidental findings. A summary of the topics and speakers follows (see the Appendix for a detailed schedule).

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| **Working Group Meeting #3 -- Developing Ethical Guidelines** | | | |
| Atlanta: October 2018 | | | |
| **Topic** | **Speaker** | **Project Role** | **Affiliation** |
| Governance and oversight | Megan Doerr  Aaron J. Goldenberg Bartha Maria Knoppers | Co-Investigator Working Group/Author Working Group/Author | Sage Bionetworks Case Western Reserve U. McGill University |
| Consent | John T. Wilbanks Eric M. Meslin | PD/PI Working Group/Author | Sage Bionetworks Council of Canadian Acads. |
| Representative samples | S. Malia Fullerton | Working Group/Author | University of Washington |
| Minority participation | Charmaine D.M. Royal | Working Group/Author | Duke University |
| Group harms and benefits | Joon-Ho Yu | Working Group/Author | University of Washington |
| Children as research subjects | Kyle B. Brothers | Co-Investigator | University of Louisville |
| Incidental findings and return of results | Susan M. Wolf Ellen Wright Clayton | Working Group/Author Working Group/Author | University of Minnesota Vanderbilt University |

Following Working Group Meeting #3, and based on feedback from the group, each author will complete a 5,000 word article describing critical challenges, identifying policies or technologies that could help address the challenges, and proposing draft language of recommendations for the Working Group.

**Stage 4:** Working Group Meeting #4, lasting one day, will attempt to achieve consensus on the key issues discussed during the first three Working Group meetings. We considered several formal consensus methodologies commonly used in health-related fields, including the Delphi method,[[52]](#endnote-53) the Nominal Group Technique,[[53]](#endnote-54) the RAND/UCLA Appropriateness Method (RAM),[[54]](#endnote-55) and the NIH consensus development conference.[[55]](#endnote-56) These methods were developed to define levels of agreement on controversial or newly-emerging topics where objective information is insufficient. Although they all generally involve organizing subjective judgments and synthesizing them with existing evidence, each method has particular advantages and disadvantages, and they are often modified to best suit the topic at hand and available resources.[[56]](#endnote-57)

We have selected RAM (with modifications) as the optimal method for building and assessing expert consensus on the appropriateness of specific approaches to ELSI issues arising in unregulated mHealth research. Traditionally, RAM has been used to assess the relative weight of the benefits and harms of a medical or surgical intervention and involves these steps: (1) perform a detailed literature review to synthesize the latest available scientific evidence; (2) produce a list of specific clinical scenarios that categorize patients who might present for the procedure); (3) identify a panel of experts, who individually read the literature review and then rate the benefit-to-harm ratio of the procedure; (4) convene an in-person meeting of the panel, during which panelists discuss the distribution of the group’s ratings for each indication, focusing on areas of disagreement; (5) provide panelists the opportunity to revise their ratings, with no attempt to force consensus; (6) classify the procedure as “appropriate,” “uncertain,” or “in appropriate” for each indication, in accordance with panelists’ median rating and level of disagreement.

The specific activities and workflow detailed in previous sections were designed to support a modified version of the RAM consensus process.

1) **Literature review and available evidence**: Working Group/Authors will be carrying out an intensive analysis of the existing literature on their assigned topic across Working Group Meetings 1-3, with the results disseminated for consideration and discussion by the larger group in the form of presentations and draft manuscripts. The Working Group will also build its knowledge base through expert presentations by special guest speakers. We will be generating additional empirical evidence through our Aim 1 in-depth interviews with thought leaders.

2) **Scenarios and indications**: Our draft Aim 1 interview guide provides an example of a multi-faceted scenario designed to raise key ELSI issues and allow exploration of pivotal factors, such as type of researcher, type of study, and type of data. This draft scenario will be further developed by the Working Group, and the issues it raises illuminated by the interviewees. This rich foundation will enable us to produce a matrix of indications and potential policy interventions.

3) **Expert panel ratings**: Working Group members will serve as our expert panel, bringing not only their own expertise, but perspectives gained through engagement in the Working Group meetings and process. Prior to Meeting #4, members will be asked to rate the policy intervention for each indication in the matrix, considering both the benefits and potential harms. Ratings will be on a 5-point scale ranging from Strongly Oppose🡪Strongly Support. The research team will tally these initial results and prepare a document summarizing the median and dispersion of each rating. We will prepare a customized version for each Working Group member that overlays his/her individual ratings on the aggregate results.

4) **In-person discussion**: During Meeting #4, the PD/PIs will moderate a structured discussion of the Group’s ratings for each indication. In particular, this meeting will focus on deliberation and exchange of ideas concerning areas of disagreement in initial ratings, as indicated by polarization at either end of the rating scale, or ratings spread over the entirety of the scale.

5) **Ratings revision**: Near the end of Meeting #4, we will provide Working Group members the opportunity to revise their ratings for each indication—with no attempt to force consensus, but rather to identify areas of agreement, minority opinions, and remaining disagreement.

6) **Classification of interventions**: Following Meeting #4, the research team will tally the final results and classify each policy intervention as “supported,” “uncertain,” or “not supported” for each indication. These results will be integral to and reported in the Working Group’s policy recommendations papers.

Following Working Group meeting #4, all authors will have an additional 6 months to revise their final articles. The articles will reflect the many disciplines of the participating authors. PD/PI Mark A. Rothstein will also draft an article to serve as a summary of the other articles and present the recommendations. This concluding article, as well as the other articles, will focus on ethics, law, and policy. In drafting the legal recommendations the PD/PI will analyze federal and state statutes, federal regulations, judicial decisions, and the legal literature. The research will utilize both print and online sources, including LEXIS/NEXIS and WESTLAW. The PD/PI has an extensive record of writing influential, concluding articles/chapters containing recommendations from diverse groups of experts. Examples include "Genetic Secrets: A Policy Framework" (genetic privacy);[[57]](#endnote-58) "Epilogue: Policy Prescriptions" (pharmacogenomics);[[58]](#endnote-59) "Policy Recommendations" (genetics and life insurance);[[59]](#endnote-60) and "Translating Values and Interests into the Law of Parentage Determination (DNA paternity testing)."[[60]](#endnote-61) Most recently, he was lead author of "Comparative Approaches to Biobanks and Privacy" (international biobank research).[[61]](#endnote-62) The genetic privacy research was funded by a grant from the Department of Energy and the other research by grants from the NIH.

**Aim 3: Educational programs and translation of recommendations.**

**Sub-aim 3-1:** *App developer workshops and videos*. To achieve a real-world impact, ELSI frameworks developed by the Working Group must gain traction in the software developer culture. Accordingly, we will hold two half-day app developer workshops in the app developer "hubs" of New York City and San Francisco. The workshops will explain and promote key principles of research ethics as well as highlight existing toolkits and resources that enable app developers to integrate protections for the welfare of research participants into their coding practices. We will recruit app developers through our strong connections to developer groups like Sensored and Quantified Self meet ups, as well as through developer lists for ResearchKit, ResearchStack, and Open mHealth. We will also recruit co-sponsors local to New York and San Francisco to leverage their developer networks and recruit attendees. The workshops will serve to catalyze best practices in a pragmatic way. Videos and other materials developed at the workshops will be placed online under liberal copyright licenses to facilitate redistribution and integration into other app development frameworks. A summary of workshop topics and speakers follows.

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| **App Developer Workshops** New York City: June 2019 and San Francisco: August 2019 | | |
| **Topic** | **Speaker** | **Affiliation** |
| Introduction to Research Ethics | Mark A. Rothstein (PD/PI) | University of Louisville |
| Open Source Toolkits | John T. Wilbanks (PD/PI) | Sage Bionetworks |
| Electronic Health Records | Joshua Mandel | Harvard Medical School |
| Genomic Information | Michelle N. Meyer | Icahn Sch. of Med. at Mt. Sinai |
| App Store Ethics Requirements | TBA | Apple and Google |

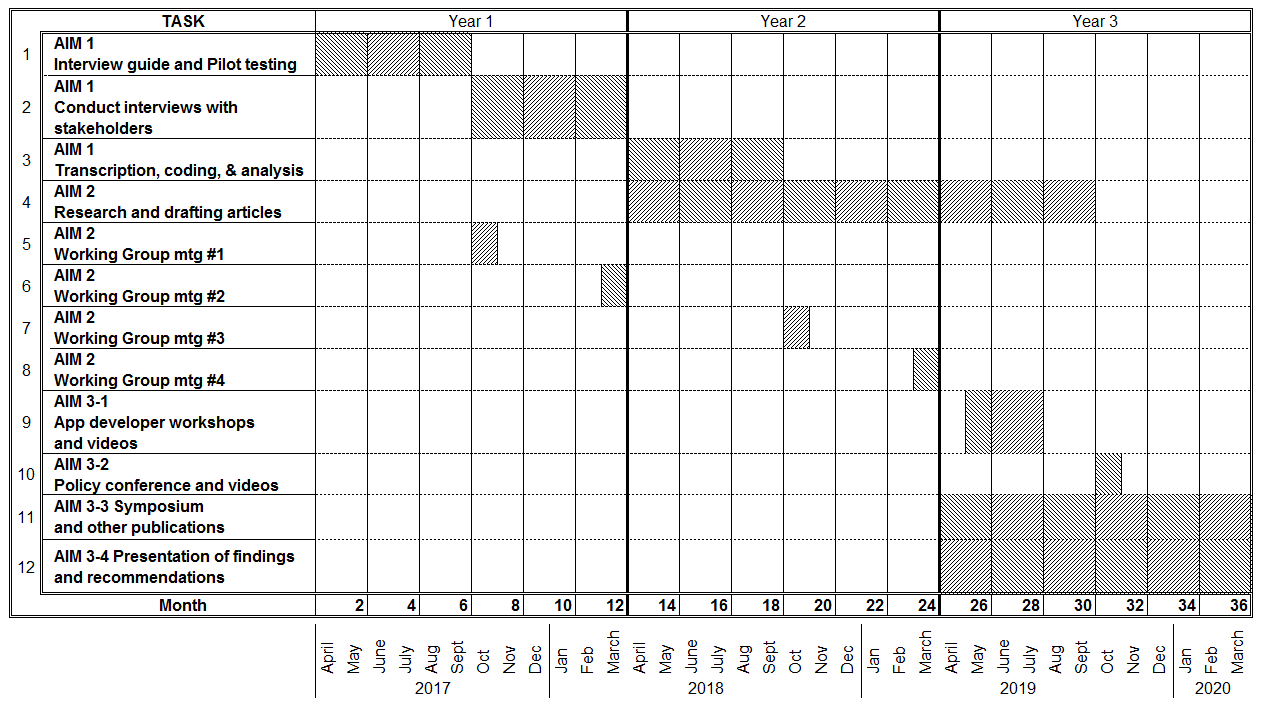
**Sub-aim 3-2:** *Policy conference and video*. Translating ethical and policy analyses into legislative or regulatory action is complicated. A key first step is informing policy makers and stakeholders about the issues and the importance of timely action. To this end, we will hold a half-day conference in Washington, DC, to focus on the public policy issues raised by unregulated health research using mobile devices. We believe that such a conference would be of great interest to the NIH, FDA, FTC, OHRP, other federal agencies, Congressional staffs, state governments, professional organizations, patient groups, researchers, IRBs, and other entities. The conference will serve to catalyze policy development and implementation. A video of the conference will be posted online.

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| **Public Policy Briefing and Conference** | | |
| Washington, DC: October 2019 | | |
| **Topic** | **Speaker** | **Affiliation** |
| Technology Introduction and Update | John T. Wilbanks (PD/PI) | Sage Bionetworks |
| Unregulated Research | Mark A. Rothstein (PD/PI) | University of Louisville |
| Thought Leader Interviews | Laura Beskow (Co-I) | Duke University |
| Panel Discussion on Key Issues: IRBs, Access to Technology, Privacy, and Data Sharing | Jeffrey R. Botkin (WG/A) Kyle B. Brothers (Co-I) Amy L. McGuire (WG/A) Heather L. Harrell (Co-I) | University of Utah University of Louisville Baylor College of Med. University of Louisville |
| Consensus Recommendations | Mark A. Rothstein (PD/PI) | University of Louisville |

**Sub-aim 3-3:** *Publication of symposium*. Working Group members and key personnel on the proposed grant will draft 20 articles containing consensus policy recommendations to be published in a special symposium issue of the *Journal of Law, Medicine & Ethics (JLME),* one of the most prestigious and widely-referenced journals in the fields of bioethics, health law, and health policy. Letters of commitment from the journal and all authors are included in the Letters of Support. The PD/PI has a longstanding relationship with this journal, having written a regular column ("Currents in Contemporary Bioethics") quarterly since 2000. The feasibility and likely success of the symposium is evidenced by the 2016 publication of two symposium issues of *JLME* (27 articles) for the NIH-funded grant, "Harmonizing Privacy Laws to Enable International Biobank Research," for which Mark A. Rothstein was the PD/PI.

**Sub-aim 3-4:** *Presentation of findings and recommendations*. The key findings and recommendations will be presented by the investigator team to a diverse group of stakeholders at major professional meetings and conferences of patients groups and policy makers. Among the audiences to be targeted: Public Responsibility in Medicine & Research (PRIM&R), the nation's leading organization of professionals in health research oversight; regional meetings of IRB officials; meetings of patient advocacy and consumer groups; and meetings and conferences that will be part of or related to the Precision Medicine Initiative.

**D. TIMELINE**



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