Research with Digital Health Methods 2.0

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Important Caveat: This is intended to be general guidance to assist investigators in navigating a complex area; it is a "points to consider" document. Unfortunately, because there are many parties at the institutions involved, the IRB is not able to propose a hard-wired, one-size-fits-all approach to follow for getting a project approved. Please note: Partners is in the process of hiring a Mobile Health App and Device Analyst that will facilitate and assist with institutional review of mobile health clinical research protocols. It is expected that this role will constitute another formal "ancillary review" like radiation safety or pharmacy review. We expect this will speed review of these projects.

Introduction

Since the PHRC guidance on Digital Health Research was issued in early 2015, this area of research has continued to rapidly evolve. New technologies allow sensing devices to collect large amounts of complex data during everyday life with minimal risk to participants, but with many questions about privacy and data uses. Though use of smartphone apps and wearables like FitBit may be frequently used in everyday life, the issues regarding the collection, transmission, use and future use of data have regulatory and institutional implications in the research context.

Digital health methods include collection, transmission and/or dissemination of private or non-private actively or passively collected data or private information using software or technology on mobile or wirelessly communicating devices such as smartphones, free-standing monitors or sensors, or wearable devices that collect information at a point in time or over a period of time. This includes:

- Homegrown smartphone apps or wearables to be potentially marketed broadly, or via partnerships with a third party (software or mobile device creators, software engineer developing digital phenotype software, smartphone app developers).
- Use of marketed and readily available apps or other software in the clinical research context, including wearables (Fitbit, other sensors worn on the body), smartphone apps that passively collect data, installation of monitors that use wireless, Bluetooth or other methods to create information about an individual over time.
- Pervasive data collection using multiple sensors or devices placed in an individual's or group's environment.

Digital Health and IRB and Institutional Review and Approval

Before IRB review takes place, it is most efficient and typically necessary that studies involving the above methods first and/or in parallel consider the following extra-IRB institutional issues.

For ALL digital health research protocols submitted to the IRB, first contact the Clinical Trials Office (CTO) and the Research Information Security Officer (RISO), so they can evaluate the methods to be used. These approvals will be required

before the study can begin, and it is most expeditious to discuss your study with them before sending to the IRB. For example, the IRB can't opine as to what the consent form should say, if the RISO office has not yet agreed that data security is acceptable, and the CTO has not agreed upon what subject level data are being shared with for-profit concerns.

non-IRB Institutional Review Considerations	Contact	Notes
Research Information Security	**RISO@partners.org** **Fabio Martins**	**Required for all digital health research protocols. Send RISO approval email with the Insight application. See detailed information below table regarding RISO review**
Contracting (Clinical Trials Office)	**avital@partners.org**	**See detailed information below table regarding CTO review. There may be other entities that are involved in contracting. CTO deals with studies where there is an interaction with a human subject for research and industry support, including "in kind" support like provision of an app.** **The IRB require CTO's approval or statement that they do not need to review for all Digital Health Research submissions. Submit approval/communication from CTO with your Insight application**

Return of information to patient/clinical staff	**Ethics and privacy issues related to sharing information are assessed during IRB review, but may require discussion with your department representatives or medical records, before submitting, or the IRB may return to ask for this input and documentation**	**Is the information collected validated for use in care, and appropriately returned to patients/clinicians for care? For example, an app collects data linked to a dashboard where the participant's regular clinician will receive data in real time. What is used in care? Is agreement required from the physicians to monitor information? Is the Department supporting the time of staff involved? What happens if the software/device malfunctions? Does an app direct a patient to take clinical action (e.g. reminder for medication or "call your doctor?").**
Placement of information in the EHR/EPIC	**Partners e-Care** **Holly Barr Vermilya** **Medical Records/HIM at your site**	**Placing information collected in research on clinical platforms or the Electronic Health Record (EHR) is a complicated matter that may require formal institutional/EPIC approval.**
Biomedical Engineering	**See Navigator Website**	**BME review is triggered as an ancillary review upon IRB submission. BME performs electrical safety assessments, and may refer to other groups (laser safety, or wireless review).**
FCC regulation issues	**Rickey L. Hampton** **Information Systems**	**Wirelessly communicating devices utilized in the hospital or elsewhere may need review by Biomedical Engineering or others to ensure safe and compliant usage in a given clinical environment (could your device or app interfere with other devices is a major concern).**
Quality implementation vs. Research activities	**Departmental or Site Quality Leadership**	**If a digital health device is being used in clinical care, as part of hospital inventory clinical discuss with your clinical leadership.** **If an app is recommended to an individual patient by a clinician, but data is not being systematically collected or otherwise monitored, and there is no research intent or collection of research data, and the technology is purchased**

		independently from an approved hospital vendor or is in routine use in care, that is not a research activity that needs to come to the IRB. **Please also review the PHRC Clinical QI Checklist and Guidance at the Navigator.**
Innovation/Research Management/CTO	**Your divisional representative in Innovation, Research Management or CTO. See Navigator.**	**For external data sharing, Research Management executes external Data Use Agreements (DUAs) related to foundations/grant-funded research. If data sharing is part of a clinical trial or MTA, CTO and Innovations respectively would include these in those contracts. Please contact the appropriate office to discuss the need for a DUA if the digital health project will share any information with an external entity (for-profit, non-profit, or academic medical center).**
FDA Oversight	**See FDA guidance on mobile health apps** **https://www.fda.gov/MedicalDevices/gitalHealth/MobileMedicalApplicatic default.htm**	**Some apps/devices may be FDA regulated (for example mobile diagnostic devices like an EKG, glucometer or oximeter app or apps that direct drug dosing).**
Partnerships with outside entities involving staff coming on site or interacting with research participants	**Maria Sundquist and Laura Kea at the IRB**	**If outside employees/collaborators plan to come on site or otherwise interact with staff or patients, those individuals may need IRB review for their work at their own institutions, and/or they may need to meet Partners' institutional requirements. Special agreements may be needed if the Partners IRB is asked to "cover" outside investigators working here or with patients elsewhere.**

Office of Interaction with Industry (OII)	**Kim Lincoln and Sharon Wilson**	**Participation in promotional activities, marketing or endorsements is generally not allowed. Contact OII.**
Public Affairs	**Institutional Public Affairs Offices**	**Companies may wish to reference your use of their software/device in marketing materials/press. Agreement of the hospital's and/or Harvard's Public Affairs offices is typically required.**

Clinical Trials Office (CTO)
Before the IRB can review a protocol using the methods described above ("Digital Health Methods"), such protocol requires the review and approval of CTO.

It is common for the owner of a Digital Health Method to require an individual to accept an agreement or terms (e.g., End-User License Agreement, Terms of Use, Privacy Policy, etc.) in order for him/her to use the Digital Health Method. CTO reviews any agreement or terms that a subject is required to accept in order to use the Digital Health Method for human subject research to ensure that requiring a subject to accept such agreement or terms does not violate:

1. federal human subject research regulations (45 C.F.R. 46.116 – "exculpatory language prohibition");
2. the HIPAA Privacy Rule; and/or
3. Other policies and guidance that may apply, e.g., readability of consent documents (8th grade reading level).

If any such agreement contains problematic provisions, such as exculpatory language (language through which the subject or his/her representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence), then CTO may need to request the removal of or negotiate the provisions of that agreement with the owner of the Digital Health Method. If the owner of the Digital Health Method does not agree to do so, then the study design may need to be changed so that the agreement is not part of the consent process.

It is important to note that if a subject has already accepted the terms of an agreement to use a Digital Health Method prior to enrollment in the study (for example they own and

use a FitBit already and will allow you to access their data), then CTO does not need to review that agreement.

The CTO also reviews the data that will be collected through a study subject's use of the Digital Health Method and who will have access to such data.

The CTO will determine whether your planned use of the Digital Health Method is acceptable per institutional requirements. CTO approval of the protocol is required for submission to the IRB PRIOR to IRB review and can be submitted with the initial submission on Insight**.**

As part of its review, CTO frequently asks the following:

1. Are subjects required to accept any agreement or terms (e.g., terms of use, privacy policy, end-user license agreement, etc.) in order to use the Digital Health Method for the study?
2. Will any party (other than the institution) have access to any data collected through a study subject's use of the Digital Health Method? If so, what data will such party(ies) have access to?

Other questions posed by CTO may concern the involvement of the owner of the Digital Health Method in the study. For example,

1. Is the owner of the Digital Health Method sponsoring the study?
2. Is the owner providing funding or support for the study?
3. Will the institution be receiving/sending study data from/to the owner?
4. Is the institution receiving the Digital Health Method from the owner at a discount not normally offered to other academic medical centers and research institutions?

Research Information Security Officer (RISO)
RISO also reviews all planned uses of the above. For each protocol, an approval e-mail from RISO (riso@partners.org) is required PRIOR to the IRB reviewing your study**.**

For example questions will include:

- Data Classification
- Data Life Cycle
    - Data Transmission
    - Data Destruction
    - Data Storage
- Access control
- Asset management
- Third-party vendors
- Security maintenance

Additional information about the review process can found:
https://rc.partners.org/research-apps-and-services/security

Other Considerations

1. Consider when Partners clinicians or staff are asked to participate as research subjects. In many digital health studies, there are both patient and clinician subjects. If clinicians are receiving information from digital health technologies used by patient participants that can or must be monitored, their time/effort and the potential risks or discomforts and benefits of being involved in the research should be discussed. Participation in research is voluntary for staff subjects as well as patient subjects.

2. A full discussion of how clinically relevant or medically actionable information collected by digital health methods will be monitored by clinicians needs to be included in your protocol (and consent form). Patient subjects will *assume* that clinicians are receiving and responding to information generated by apps that are provided by, or recommended by, our clinicians, *unless it is explicitly clarified that this isn't the case*. Participants in general need to understand who sees what data, when, and how it is to be acted upon, or not. Risk management considerations in the context of varying state laws may apply in some scenarios. For example, an app monitoring behaviors consistent with a manic episode or epileptic seizure raises questions about who's reviewing this information, and when, and what action will be taken by providers. Additional considerations arise when study participants are out of state. For example,, an automated glucometer might indicate impending ketoacidosis, or an app used in the hospital might collect data might suggest or confirm that a medical error was made. Please consider in a 360 degree fashion the implications of the collection and sharing of data in a given study. In addition, fully address any issues related to the potential for malfunction (e.g. poor wireless connection, other glitches) and how this is to be handled. If your application does not discuss these issues, it will be returned to you with questions.

3. Include information about the manufacturer, the app/device, if applicable, such as a device brochure, manufacturer's information, printed screenshots, or other information that will be useful for reviewers. Please avoid the use of web links to manufacturers' websites, which may change or outdate.

Artificial Intelligence/Machine Learning

We appreciate this is a new and rapidly developing field in diagnostics, therapeutics and prediction/cost modeling, that will require the use of large and comprehensive datasets. Much of this work will be "simply" medical records research, though if industry-sponsored, CTO issues still apply. The IRB will consider these projects carefully and engage the relevant groups above. There are institutional, privacy/identification, and cost/valuation issues related to release/sharing of large datasets and "warehouses." When methods are introduced into the testing/validation phase, there may be other considerations related to how the information is being used clinically. Investigators should discuss what evidence supports validity and reliability.