Mobile Apps: Considerations for Use in Research Involving Human Subjects

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About Today’s Presenters

Michele Russell-Einhorn, JD
Chief Compliance Officer and Institutional Official, Advarra

- Chief Compliance Officer and Institutional Official
- Co-Chair, Subpart A Subcommittee, SACHRP
- Founding member, NCCN IRB Directors Forum
- Previously served as Senior Director, Dana Farber Cancer Institute, Office for Human Research Studies
- Lawyer by training
About Today’s Presenters

Robert Neff
Director for Innovative Technology Solutions, Thomas Jefferson University

- Team builds applications for healthcare and research for use cases across the university and health system
  - Solutions include mobile apps for collecting data for clinical research in IRB approved studies
- Team understands how to develop for the complex environment of consumer facing healthcare solutions
Objectives

- Outline a general definition and overview of mobile apps and mobile medical apps
- Describe the questions and issues mobile apps and mobile medical apps raise in research involving human subjects
- Identify issues that need to be considered by IRBs when reviewing research that includes a mobile app
Mobile Apps and Mobile Medical Apps Overview
What Are Mobile Apps Generally?

- Mobile apps are software programs which are designed specifically for mobile devices such as phones or tablets.
- Examples of mobile apps:
  - Uber, Google Photos, Camera App, WhatsApp, Fitbit
- Most mobile apps are part of an ecosystem which may include web applications, hardware, and even physical services.
What Are Mobile Medical Apps?

Mobile **Medical** Apps are apps that meet the statutory definition for a device. They are those apps which have the purpose of monitoring, improving or otherwise affecting one’s health.

Examples of these apps are:

- Fitbit, Apple Health, Clinical Surveys, Video Visits

FDA Guidance on Mobile Apps

FDA regulates a subset of mobile apps which meet the definition of “mobile medical app.” FDA has stated that the agency intends to exercise enforcement discretion with respect to mobile apps that may meet the definition of medical device but pose a low risk to participants.

**High risk MMA examples**
- An app that monitors blood pressure and transmits the data to a treating physician
- An app that controls the delivery of insulin through an insulin pump

**Low risk MMA example**
- Apps for recording patient diet and exercise habits

Whether or not a mobile app is FDA regulated or approved not should not be the primary factor in considering its use in research.

The questions here will help guide a decision regarding the risks of using a specific app in research, whether or not it is one which is under the regulation of the FDA.
Considerations for Researchers

The first question to help orient yourself, prior to the key considerations, is whether your research involves the evaluation of the app itself, or is leveraging the app to evaluate something else.

There are five core areas to understand before designing research on or with mobile apps:
1. General Considerations and Risks
2. Technology
3. Data Security and Confidentiality
4. Consent and Terms of Use
5. Support and Training
General Considerations and Risks

There are considerations and risks in any clinical research or study which carry over to mobile app and digital studies.

Some of these common and still pertinent risks include:

- What data will be collected?
  - Research data?
  - Incidental data captured by the app?
- Is data collected identified or de-identified?
- Where will data be sent? (Medical records?)
- What are the risks to privacy and confidentiality?
- What are the risks of the app not working as intended?
- Are there costs to the participant for using the app?
- Is the app content (font, language, videos) appropriate for the participant population?
In some cases the app being studied or used in a study is one which is created expressly for that trial. In these cases, since the app is custom built, extra precautions including adhering to best practices in software development should be in place.

Commercially built apps remove the development burden from the researchers, however they present their own concerns.

Some high level concerns for technology include:
- How will the researchers access the data?
- Will devices be provided or will participants have their own?
- Do participants use their own logins and accounts?
- What types of devices will be supported?
- How will software updates, new phones and study cancellation be handled?
Example: Technology Concern

A study in which participants are asked to report their mood via a survey app reminds participants to complete a survey every three hours. The researchers start seeing negative impact on participants who are monitoring their mood so often. The researchers would like to stop the study, however the mobile apps keep reminding participants to complete a survey.

Some things to consider:

▷ Should the app have the ability to be remotely reset or stopped?
▷ Are the researchers now required to review data in real time from the remaining participants?
▷ If the app is disabled remotely, how will that be communicated to the researchers?
Data Security and Confidentiality and Access to Data

The security of data and the need for participants to be and feel confident in the handling of their information is critical in promoting their willingness to participate in research and clinical trials. It is also required by law. With digital technologies, there are often many parties involved, so ensuring data security is even more important and challenging. Ensuring that only authorized researchers have access to the data is critical.

Considerations include:

- What mechanisms are in place to minimize risks to confidentiality? Where is data stored? Is it encrypted?
- What passwords or pins are used for the participants and investigators?
- What auditing is available on who accessed the data?
- How is access to third parties evaluated and restricted?
- Is the device itself collecting data?
Informed Consent

How is consent obtained?

1. eConsent?
   • Is it combined with the mobile app?
   • Does it contain all elements of informed consent?
   • Is there an option to use written paper consent instead?

2. Waived consent?

3. Written paper consent only?
Terms of Use

In addition to consent, there may be legal terms related to the technology (terms of use, license agreements, privacy policies, etc.) that the participant must accept in order to use the app.

Questions include:

- How is the information explained to the users? (These agreements are often just clicked through)
- Does the content comply with applicable research regulations?
- Is there any information in the agreement that should also be included in the consent form (e.g., access to data)?
Support and Training

Mobile apps are much easier to use than traditional software, but it is a misnomer to believe that they don’t require support or training. Even the easier apps will cause confusion for some users, or fail (sometimes due to external factors).

Some common and pertinent risks here include:

- How will participants get support for the technology (both at study start and ongoing)?
- How will password resets be handled?
- Is there any monitoring in place to ensure the technology is working?
- Who is providing all of this support? What hours?
Example: Support and Training

A study in which participants are asked to report their mood via a survey app reminds participants to complete a survey every three hours. The researchers start seeing negative impact on participants who are monitoring their mood so often. The researchers would like to stop the study, however the mobile apps keep reminding participants to complete a survey.

Some things to consider:

- How to handle cases where the participant is not receiving notifications to complete the survey as expected?
- How will cases of a participant switching to a new phone/device be handled?
- What should a participant do if the app repeatedly crashes and they are unable to complete all required surveys?
- Will training or documentation be available for researchers on how to access the data?
In-Depth Discussion of IRB Issues
1. Risks to subjects are minimized.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.
3. Selection of subjects is equitable.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by §46.116.
5. Informed consent will be appropriately documented, in accordance with and to the extent required by §46.117.

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
   
   b. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.
...no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the **legally effective informed consent** of the subject or the subject's legally authorized representative.

An investigator shall seek such consent only under circumstances that:

- Provide the prospective subject or the representative sufficient **opportunity to consider** whether or not to participate and that minimize the possibility of coercion or undue influence.
- The information that is in a language understandable to the subject or the representative.
- No informed consent, whether oral or written, may include any **exculpatory language through which the subject or the 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.**
General Requirements for Informed Consent

1. A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed and identification of any procedures which are experimental;
2. A description of any reasonably foreseeable risks or discomforts to the subject;
3. A description of any benefits to the subject or to others which may reasonably be expected from the research;
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;
General Requirements for Informed Consent

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject; and

8. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
Additional Elements When Appropriate

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

3. Any additional costs to the subject that may result from participation in the research;

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

6. The approximate number of subjects involved in the study.
Criteria to Waive Informed Consent

✓ Minimal risk research
✓ Waiver or alteration will not adversely affect the rights and welfare of the subjects
✓ Subjects will be provided with additional pertinent information
✓ Research could not practicably be carried out without the waiver or alteration

*Regarding the word “practicable”
SACHRP recommendation:
“Practicability” for the purposes of analyzing waiver applications should include considerations of scientific validity of studies, and of how studies involving huge subject populations, a significant portion of whom would be lost to follow up and not reachable, might be compromised if consent were required. Real world big data studies would be prime examples of studies whose validity would be undermined by a requirement that consent be obtained, when obtaining consent from even a major portion of subjects is not reasonably possible or feasible.
Considerations When a Research Protocol Includes Use of a Mobile App

1. Is it a clinical investigation subject to FDA oversight?
2. Is there federal funding?
   • Does it meet the definition of research involving human subjects?
   • Is it exempt? Can it be expedited? Does it require full Board review?
3. If it is not subject to FDA oversight, and there is no federal funding, what regulations or criteria (if any) will be applied?
Range of Types of Mobile Apps

Fitbit ➔ blood pressure monitor ➔ regulates insulin pump

Standalone ➔ key component of an intervention
mobile app ➔ clinical trial
Considerations When a Research Protocol Includes Use of a Mobile App

Assuming it is subject to, or guided by, either FDA oversight or Federal Regulations for the Protection of Human Subjects in Research or those regulations:

1. What information should be provided to the IRB to ensure the ability to adequately review the research?
2. When is expedited vs full board review appropriate?
3. What issues should be addressed in the review process?
What Information Needs to be Provided to the IRB?

1. **What is the use of the app in the research?**
   - To determine the validity of the app (controls delivery of insulin through an insulin pump)
   - To collect, store or transmit participant data (app collects patient recorded outcomes through surveys)
   - To provide logistical support but does not collect, store or transmit participant data (e.g., app sends reminders to take a study drug)
What Information Needs to be Provided to the IRB?

2. Who is the user population?
   - Only individuals who own iPhones or Apple watches
   - Only individuals of a certain age range

3. Does use of the app require use of a specific device (e.g., iPhone or Apple watch)?
   - Are participants given a device?
     - Cost to receive the device?
     - Logistics to return device?
   - Do participants use their own devices?
     - What happens if the device is not working? Whose responsibility is it to fix it?

4. Is use of the app mandatory or optional?
   - If the app is optional, what are the alternatives to using it? (Phone calls vs app reminders to take a drug)
What Information Needs to be Provided to the IRB?

5. Is it a custom-made app? If so, what testing has been done regarding functionality, compatibility, performance, stability, and security?
   • What is the information that needs to be provided?
   • What is the expertise necessary to make these determinations?

6. If a participant withdraws, how is withdrawal implemented? Is the app withdrawn from the device?

7. Are participants required to agree to any end user agreements, terms of use or privacy policies in order to download or access the app?
   • If so, these must be provided to the IRB for review
8. Who has access to data collected by the app? Does the device itself have access to the data?
9. How/where is participant data stored?
10. What are the risks of the app not working as intended?
11. What support is available for technical questions?
12. Does the app capture incidental data about participants (e.g., location)?
**Expedited vs Full Board Review**

**Expedited**
Mobile apps or mobile medical apps not under FDA oversight or subject to FDA enforcement discretion could be expedited if they fall into a category on the expedited review list

- For example, an app that notifies participants that it is time to take a medicine

**Full Board**
All other research involving mobile medical apps need to be reviewed by the full convened IRB

- FDA guidance states that non-significant risk vs significant risk determinations should be made by the full convened IRB
What Should IRB Reviewers Focus On?

The IRB reviewer should have access to information sufficient to determine whether the research meets the criteria for IRB approval of research.

Specific regulatory criteria which may be most impacted by the use of the mobile app include:

• Risks to subjects are minimized
• Adequate provisions to protect privacy and maintain confidentiality
• Consent process and content is appropriate, including:
  - Alternatives
  - Costs
  - Risks
  - Confidentiality
  - Contact information (Technical support information needed?)
  - Procedures for ending participation
What Should IRBs Do with Terms of Use, Privacy Policies and License Agreements?

- Challenge is that the documents are not always research-specific and are not written with research regulations in mind
- Relate to the devices on which apps are downloaded
- Different priorities and objectives between commercial technology and research
- These documents require IRB review because they are participant-facing, participant-impacting materials and may include information that would impact a participant’s decision on enrolling in the study
  - For example: location tracking, use of data for other purposes
What Should IRBs Do with Terms of Use, Privacy Policies, and License Agreements?

- IRBs should ensure that the consent form informs participants what they will need to agree to in order to use the app and explain the consequences of declining.
  - If use of the app is required in the research:
    “As part of this research study you will need to use the XYZ App. In order to use the app you will be asked to agree to the Terms of Use which will appear on your mobile device’s screen when you first start using the app. If you decide that you do not want to agree, then you should not participate in the research.”
  - If use of the app is optional in the research:
    “As part of this research study you will have the option to use the XYZ App. In order to use the app you will be asked to agree to the Terms of Use which will appear on your mobile device’s screen when you first start using the app. If you decide that you do not want to agree, then you can chose not to use the app and still participate in the research.”
What Should IRBs Do with Terms of Use, Privacy Policies, and License Agreements?

IRBs should check to see if the Terms of Use includes key information that also needs to be included in the consent form.

- Information about data collection, privacy, and confidentiality is often buried in these documents—as well as exculpatory language.
- The consent form should point this out, particularly since users typically click through these documents and may miss the information.
- Example of consent form statement:
  “While using the app data about you, including personal health information, location, and internet usage will be collected and transmitted to the researchers and may also be transmitted to people outside of the research study. A complete description of this data collection and sharing is found in Terms of Use. The Terms of Use provides instructions on how to request deletion of your personal data if you decide to do that in the future.”
What Should IRBs Do with Terms of Use, Privacy Policies, and License Agreements?

Regulations prohibit “any exculpatory language through which the subject or the 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.” (45 CFR 46.116 and 21 CFR 50.20)

- OHRP and FDA consider exculpatory language to be language which has the general effect of freeing or appearing to free an individual or an entity from malpractice, negligence, blame, fault or guilt
- IRBs should review the documents to ensure that they do not include any exculpatory language
- These documents are often difficult to revise because they are for general use and are not specific to the research. Therefore, an alternative to consider is inserting additional language into the consent form that explicitly addresses the issue in the context of the research.
  - Example: “While the Terms of Use may include statements limiting your rights if you are injured in this study, you do not release the investigator, sponsor, institution or agents from responsibility for negligence and these statements do not apply to the use of the app in this research study.”
## Investigator Issues

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<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Access to larger participant population</td>
<td>Significant time responding to participant questions about meaning of data</td>
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<tr>
<td>Faster recruitment</td>
<td>Significant time to respond to participant app or device trouble-shooting needs</td>
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<td>For clinical trials research, decreased number of in-person visits to site</td>
<td>Logistical challenges if devices need to be replaced or returned</td>
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<td>Additional information in consent forms that provide more background detail and definitions relating to the research</td>
<td>Data attribution concerns</td>
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<td>Costs for devices and data storage</td>
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Participant Issues

<table>
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<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Access to real-time data</td>
<td>Inadequate support for problems with app or device</td>
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<tr>
<td>Reduced visits to clinics</td>
<td>Inadequate feedback regarding the data that is collected and participants situation</td>
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Example of Unexpected Issue

The mobile app provides for an alert or a notification. Protocol and consent are silent regarding what options exist when a participant ignores the alert or notification.
Equitable Selection of Subjects

1. What is the language of the app?
2. Is written consent an alternative?
3. How do you confirm who is actually enrolling in the research?
   - Minors?
   - Prisoners?
   - Cognitively impaired individuals?
Conclusion

- Research using mobile apps can provide access to significant larger participant populations
- It is not without its challenges
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