Mobile Software Applications and Wearables That Are Regulated Medical Devices in Human Subjects Research

The purpose of this guidance is to help NC State University researchers understand when wearables and mobile software applications become medical devices, are subject to regulation by the Food and Drug Administration (FDA), and what the NC State IRB application process and expectations are for these mobile software applications and wearables that are medical devices in human subjects research. Different types of research design (i.e., phased research, clinical trials) and content areas (i.e., biomedical engineering, exercise science, veterinary medicine) are covered in this guidance, and appendices provide links to required forms and templates.

Definitions

Before we get started on what the NC State University IRB's expectations are for research with mobile software applications and wearables that are regulated medical devices, it's important to define our terms.

Mobile Software Applications

A mobile software application is a software application that can run on a portable platform such as a smartwatch, smartphone, tablet, or other mobile communication device. Some mobile software applications are designed to be used to be used only on one portable platform (e.g., iOS for iPhone, Kindle Fire OS) while others can be used on multiple types of platforms because they are designed to use cloud or web technologies instead of specific hardware/software combinations that a single platform application utilizes.

While it is common to think that a mobile application is always internal to a device, some mobile applications attach physically to a mobile device. If you've ever purchased something at a store or a craft market by swiping your debit card into a Square card reader plugged into a smartphone, the Square card reader is a mobile application that is connected to the phone, WiFi, and other platforms to be able to process your payment to the merchant.

Other mobile software applications connect wirelessly with other hardware and software using Wi-Fi, Bluetooth, or USB to create a complete operating system. An application on your phone to close your garage door or to start your car's engine are two examples of mobile software applications that are combination devices.

Wearables

A wearable is something that a human puts on their body that collects, transmits, and sometimes analyzes data in real time. Some wearables connect to Wi-Fi and/or Bluetooth while data is being collected or transmitted; other wearables require the user to plug the wearable in via a hardwire connection to transmit the collected data from the wearable to another software platform or device.

Wearables can include items such as smart clothing that logs the wearer's motion or body temperature, smart glasses that tracks the wearer's eye movement, smartwatches and Oura rings that track user's heart rate or electrical activity, and wearable cameras such as GoPro.

Wearables often, but not always, work together with one or mobile software applications to function. For example, data collected by smartwatch a wearer's physical activity could be shared to a fitness or calorie tracking application on the user's smartphone.

General Wellness Products

General wellness products can be medical devices, mobile software applications, or tools that are intended to encourage or support users live a healthy lifestyle. Mobile software applications that are general wellness products include those that track

physical exercise, food/calorie intake, water intake, sleep cycles and snoring, and menstrual cycles. The intention in tracking these activities is to promote or maintain wellness. If the mobile software application tracks the same activities but uses the tracking to diagnose a disease or condition, or treat, monitor, or prevent disease in humans or other animals, then the application is not a general wellness product. More information about general wellness products can be found in the FDA's guidance document General Wellness: Policy for Low Risk Devices Guidance for Industry and FDA Staff (PDF file).

Wearables that track body activity, sleep cycle, hydration, and nutrition can be considered general wellness products if, like mobile software applications, their intended use is to support a healthy lifestyle. Some examples of wearables that are considered general wellness devices include smartwatches that solely focus on wellness strategies (e.g., step count) and physical performance optimization (e.g., encouraging daily physical activity), smart clothing that tracks physical movement, smart headband that tracks skin surface tension to prompt users to relax via meditation.

If the intended use is to diagnose, manage, treat, or prevent a disease (e.g., diabetes, kidney failure, pregnancy) through physical activity and nutrition tracking, the wearable does not qualify as a general wellness product.

Medical Device

A medical device is defined in U.S. federal law (Food, Drug, and Cosmetic Act (FD&C Act), Section 201(h)) as:

> "An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—
>
> 1. recognized in the official National Formulary or the United States Pharmacopoeia, or any supplement to them,
>
> 2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
>
> 3. intended to affect the structure or any function of the body of man or other animals,
>
> and which does not achieve its primary intended purposes through chemical action within or on the body and is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

In summary: a mobile software application or wearable becomes a medical device if it is something that is intended for medical use either because it is listed in the National Formulary or United States Pharmacopoeia, diagnoses disease or other conditions,

cures, mitigates, treats, or prevents disease in humans or other animals, or affects the structure or function of the body in ways other than drugs do (i.e., chemical or metabolic action). The definition from the FD&C Act is broad and emphasizes the intended use to determine if a mobile software application or a wearable is a medical device rather than focusing on how the item will be used in a research study.

Medical devices can be single use items or reuseable and can function outside, on, or in the body. Some single use medical devices are syringes, needles, IV bags, exam gloves and gowns, masks, and Band-Aids. Examples of reusable medical devices include surgery instruments, ultrasound machine, and MRI machine.

At NC State University, any human subjects research that plans to use a device that meets one or more of the federal criteria for a medical device is considered “proposing research with a medical device.” Whether a study that uses a medical device is also subject to additional regulation by the FDA, depends on whether the medical device is the object of study where the device is being tested for safety or efficacy (this is regulated by the FDA) or if the medical device will be used only as a tool for data collection (this type of work is not regulated by the FDA).

If a device meets the federal criteria of a medical device and will be the object of the study looking at the device’s safety or efficacy, the research team must comply with all applicable FDA regulations for research with medical devices. The regulatory requirements vary depending on the device class (I, II, III) and the risk assessment (non-significant risk device, significant risk).

At NC State University, the IRB only reviews and approves medical device research with “non-significant risk” devices. If an NC State researcher proposes a study with a “significant risk device” and the research is cooperative, the NC State IRB will rely on the research collaborator’s IRB to be the IRB of Record if e appropriate. If the research is not cooperative or the external IRB lacks the expertise to serve as the IRB of Record, the NC State researchers will work with the NC State IRB and the WCG private IRB for review and approval of the project.

Risk determinations are made by the NC State University IRB or the U.S. Food and Drug Administration (FDA). The subsequent few sections will discuss risk classifications, device types, and different approval processes that apply to mobile software applications and wearables that are medical devices.

Risk Classifications

Every medical device that is regulated by the FDA must have a risk determination. A medical device’s risk determination can be “non-significant risk” (i.e., NSR) or “significant risk” (SR). The risk determination is made by either the FDA or the NC State IRB convened full board – not the principal investigator, research team, or device inventor (though they provide their own assessment of the device for consideration by the IRB and/or FDA).

Non-Significant Risk Devices

Non-significant risk (NSR) medical devices fit into Class I or II discussed previously and where the risk of harm during use is no more than moderate. These devices can be used as tools in research or, if being tested for safety or efficacy alone or in combination with other devices (including mobile applications and/or wearables) are eligible to apply to the IRB and request an abbreviated investigational device exemption (abbreviated IDE) determination from the convened full board as part of their IRB review process.

Significant Risk Devices

Significant risk (SR) medical devices fit into Class III because they are implants, support or sustain life, or are incredibly risky to use with the potential to cause deadly harm. Significant risk devices that are being tested for safety or efficacy will need to apply to and be approved by the FDA for an investigational device exemption (IDE) alongside IRB review and approval. The NC State University IRB sends all significant risk medical device research that requires an IDE from the FDA to a private IRB for IRB review and approval.

Device Classifications

In addition to the medical device's risk classification, all medical devices also hold a classification level: Class I, Class II, or a Class III device. The device classification level does not change the IRB's protocol approval criteria or decision-making process, but it does inform what requirements and restrictions (i.e., "regulatory controls") the research team has with a medical device's use.

Class I

Class I medical devices are non-significant risk devices where there is a low risk of illness or injury caused by device use and there is a predicate device that is already on the market. Some examples of Class I medical devices include fall protection harness, gait and motion analysis that is not diagnostic, manual wheelchair, stationary bike if intended for general fitness use only, passive prosthetic limb, prosthetic socks and liners, elastic bandages, disposable exam gloves, dental floss, electric toothbrush, heating pad, ice pack, menstrual pads, and prescription eyeglasses. It is tough for wearables to fit into Class I because there usually isn't a predicate device.

Class II

Class II medical devices are non-significant risk devices where there is a moderate risk of illness of injury caused by device use. Some Class II devices are heart rate monitors, spirometers, pulse oximeters, EMG systems, BioDex, functional prosthetics with powered or joint movements, smartwatches with an FDA-cleared electrocardiogram (ECG) feature (e.g., Apple Watch Series 4 or greater), Samsung Galaxy with ECG), treadmills with diagnostic features or intended for medical or therapeutic use, diagnostic x-ray machines, surgical robots, inhalers for asthma, power wheelchairs, alcohol breathalyzer, teeth fillings, hearing aids, most contact lens types (extended wear/overnight lenses

are Class III), condoms, tampons, and pregnancy test kits. Class II medical devices have to prove safety and effectiveness prior to being able to be marketed and sold to the general public.

Class III
Class III medical devices are significant risk devices that present the potential for serious harm to one's health, safety, or welfare during device use. A few examples of Class III medical devices are breast implants, cochlear implants, implantable spinal cord stimulators, heart pacemakers, cardiovascular stents, and prosthetics implanted into the bone. Like with Class II devices, Class III medical devices must prove safety and effectiveness to the FDA prior to being marketed and used by the general public.

FDA Submission Types
If a mobile software application or wearable meets the FDA's definition of a medical device and the device class is Class II, Class III, or an undetermined class due to the device's novelty, an application might need to be submitted to the FDA for the device's use even if the use will be limited to the research study. The application submission types are a 501(k) clearance (opens in a new window), De Novo classification request (opens in a new window), premarket approval (PMA) (opens in a new window), and investigational device exemption (IDE) (opens in a new window)

501(k) Clearance
A 501(k) clearance is when a mobile software application or wearable that meets the FDA's definition of a medical device, is a Class II device, and is "substantially equivalent" to a "predicate device" that is already approved by the FDA to be legally marketed. The 501(k) clearance is given by the FDA, not the IRB, and requires specific information and additional processes to be given to the FDA. IRB review and approval always occurs before any human subjects research, but IRB review can occur after the 501(k) submission if the 501(k) application doesn't require clinical data.

Once a mobile software application or wearable receives a 501(k) clearance, the medical device is "cleared," not "approved," by the FDA. Cleared mobile medical applications will be listed in FDA's 510(k) database (opens in a new window) database and on the FDA's Registration & Listing Database (opens in a new window). It is unusual for a wearable to receive a 50(k) clearance because few wearables have a predicate device.

A few examples of 501(k) mobile software applications and wearables are:

- Digital blood pressure monitors
- Smartwatches with an ECG (electrocardiogram) function
- Wearable fall detector

- Mobile software application or wearable that helps a person manage their diabetes

De Novo

A De Novo classification by the FDA is for a mobile software application or wearable that meets the FDA's definition of a medical device, is considered to be low risk (i.e., either Class I or Class II), and there is no predicate device that is already on the market. For these devices, the research team must go through the De Novo classification request process with the FDA, which requires clinical data on the device's safety and effectiveness within its intended use. Because the De Novo application requires clinical data, IRB review and approval is usually obtained before the De Novo application is submitted to the FDA.

Some examples of De Novo submissions include:

- Mobile software applications that deliver therapeutic interventions such as cognitive behavioral therapy to individuals with a substance use disorder to assist them in abstinence from the substance the individual struggles with and increase compliance with outpatient treatment. One example of this is the Reset application (opens in a new window).

- Augmented reality (AR) and virtual reality (VR) software that provide three dimensional (3D) visualizations of anatomy (both human and other animals) for surgeons to plan their surgeries or overlay images during surgery to guide procedures. One example of this is the xvision Spine system (XVS) (opens in a new window).

- Smartwatch, such as the Apple Watch Series 4 ECG feature (opens in a new window), that integrated a diagnostic electrocardiogram (ECG) detecting heart rhythm abnormalities into a wearable

Premarket Approval (PMA)

Premarket approval by the FDA is required for a mobile software application or wearable that meets the FDA's definition of a medical device and is determined to be a significant risk device. IRB review and approval and an investigational device exemption (IDE) determination by the FDA always occurs before the PMA submission, as clinical data about the device's safety and efficacy must be submitted with the application. Receipt of an IDE from the FDA occurs BEFORE IRB approval for significant risk devices. Once the IDE from the FDA is granted and IRB approval is acquired, the PMA can be submitted.

Mobile software applications and wearables that are medical devices and went through the PMA process are listed in FDA's PMA database (opens in a new window) and on the FDA's Registration & Listing Database (opens in a new window). It is **quite rare** for a mobile software application or a wearable that is a

medical device to need a PMA because the device must be significant risk, sustains or supports human life, or if it could cause severe injury or death.

Medical device examples that would go through the PMA process are:

- A mobile software application paired with a sensor or attachment could diagnose a life-threatening condition and misdiagnosis would cause severe harm to the user

- A wearable or implant device that sustains or supports life and can only function if the software works to assess physiological function and responds accordingly, such as a ventilator or an implanted cardioverter-defibrillator

Investigational Device Exemption (IDE)

An investigational device exemption (IDE) is required for any mobile software application or wearable that is a medical device that is either significant risk (SR), nonsignificant risk (NSR) but will be used off-label in the study, or is not approved or cleared by the FDA to be used with humans for the purpose of collecting safety or efficacy data (cf. 21 CFR Part 812 – opens in a new window).

The following processes apply for all medical device studies that need an IDE:

1. The research team submits an IDE application to the FDA.

2. An IRB reviews and approves the study after the IDE application was approved by the FDA. These studies are typically reviewed by the WCG IRB per institutional policy (Word document) at the expense of the research team.

3. Informed consent must be sought and documented from all research participants (cf. 21 CFR 50 – opens in a new window)

4. The medical device must be labeled with the following verbiage: “CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use.” (cf. 21 CFR 812.5 – opens in a new window)

5. Continuous monitoring must be done alongside progress reports, a final report, and adverse event reports to the FDA (cf. 21 CFR 812.46 – opens in a new window, 21 CFR 812.140 – opens in a new window, 21 CFR 812.150 – opens in a new window, 21 CFR 812.20(b)(3) – opens in a new window)

6. The medical device must be manufactured under specific controls and its quality monitored which includes the following:

    a. Design controls (cf. 21 CFR 820.30 – opens in a new window)

b. Production and process controls (21 CFR 820.70 – opens in a new window)

c. Purchasing controls (21 CFR 820.50 – opens in a new window)

d. Quality monitoring and feedback controls (21 CFR 820.20 – opens in a new window, 21 CFR 820.90 – opens in a new window, 21 CFR 820.100 – opens in a new window, 21 CFR 820.198 – opens in a new window, 21 CFR 820.250 – opens in a new window)

e. Recordkeeping requirements (21 CFR 820.180 - 820.198 – opens in a new window)

f. Software standards (cf. FDA Guidance on Mobile Medical Applications – opens in a new window)

An approved investigational device exemption (IDE) allows an investigational device to be shipped legally and used in a clinical study for the purpose of collecting safety and effectiveness data. Investigational use under an IDE includes clinical evaluation of device modifications or new intended uses of legally marketed medical devices. Clinical studies that use investigational devices are most often conducted to support a premarket approval (PMA) and De Novo applications to the U.S. Food and Drug Administration (FDA), but only a small percentage of 510(k) clearances require clinical data to support their FDA application.

When a study uses a legally marketed medical device in accordance with its approved labeling, is studying consumer preferences, or when a medical device that will be used is NOT being assessed for safety and efficacy, the study is considered “exempt” from the IDE regulations. Although a research study can be “exempt” from the FDA’s IDE regulations, the study may still be subject to compliance with the federal human subjects research regulations.

When a medical device(s) is/are not “exempt” from FDA regulation, the research team must either obtain an approved IDE from the FDA or an abbreviated IDE from NCSU IRB before a research study with human subjects is initiated. The FDA grants IDEs for research with significant risk medical devices, while the NC State IRB convened full board can only grant an abbreviated IDE for research with non-significant risk research. If a study needs an IDE for one or more of its medical devices to be used in the research study, the FDA must grant the IDE before the IRB will approve the study. The FDA’s IDE application is separate from the NC State IRB application and so too is its review and approval timeline.

IRB Submission Types

All regulated research at NC State that involves humans and medical devices is reviewed by the IRB office even if the use of medical device doesn't require an application to the U.S. Food and Drug Administration (FDA). For studies with medical devices that are exempt from the FDA's IDE regulations, the NC State IRB does not decide whether the medical devices are significant risk or nonsignificant risk. In all reviews, the NC State IRB does, however, determine whether the study itself is minimal risk or more than minimal risk and the IRB does review the study in accordance with the federal regulations for human subjects research before the investigation may begin.

Exempt from Investigational Device Exemption (IDE) Requirements

Some medical device studies subject to IRB review are exempt from investigational device (IDE) requirements if the device is a non-significant risk as determined by the FDA and meets one of the following criteria:

1. The medical device is already approved by the FDA and the research team's planned use of the medical device falls within the condition, treatment, and population specified and either approved or cleared by the FDA via the product's labeling. (cf. 21 CFR Part 812.2(c)(1)&(2) – opens in a new window)

2. The medical device is a noninvasive diagnostic device which is not used diagnostically without confirmation by a separate established procedure AND does not require any invasive samplings or introduction of energy into the body. (cf. 21 CFR Part 812.2(c)(3) – opens in a new window)

3. The medical device is not being tested for safety or efficacy, but as a tool for data collection or consumer preference testing. (cf. 21 CFR 812.2(c)(4) – opens in a new window)

4. The medical device is for veterinary use only or for use with laboratory animals and properly labeled (cf. 21 CFR 812.2(c)(5) & (6) - opens in a new window)

5. Purpose-built devices for a specific individual that are not intended for commercial distribution or marketing on a case-by-case basis. (cf. 21 CFR 812.2(c)(7) - opens in a new window)

Please note that even if a medical device is exempt from IDE requirements, that does not mean that the study:

- does not have to follow other applicable FDA regulations;
- does not need to apply to the IRB (an IRB application is usually required!); or
- is eligible for exempt level of IRB review (it usually isn't!).

Abbreviated Investigational Device Exemption (Abbreviated IDE)

Medical devices eligible for an abbreviated investigational device exemption (abbreviated DE) from the NC State IRB convened full board are those that are

deemed to be a nonsignificant risk (NSR) device. To know if a medical device will be eligible for an abbreviated IDE, researchers must know what the intended use of the device is, what the study design is, what the device's risk assessment is per the sponsor and IRB office, and if the medical device is cleared or approved by the FDA and for what conditions and uses. If questions remain, researchers can consult the FDA guidance "Significant Risk and Nonsignificant Risk Medical Device Studies" (PDF file).

Studies that require an abbreviated IDE will be reviewed by the NC State University IRB's convened full board who will make three determinations: IRB approval, device's risk determination, and if the device will receive an abbreviated IDE.

If a device is eligible for an abbreviated IDE, the study is required to meet the following requirements:

1. The study must be reviewed and approved by the IRB (cf. 21 CFR Part 56 – opens in a new window)

2. The study must seek and document informed consent (cf. 21 CFR Part 50 – opens in a new window)

3. The medical device must be labeled with the following verbiage: "CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use." (cf. 21 CFR Part 812.2 – opens in a new window)

4. The study sponsor is required to monitor the device's investigational use to ensure participant safety and regulatory compliance (cf. 21 CFR Part 812.46 – opens in a new window)

5. The research team must maintain and provide specific records and reports to the FDA and comply with any inspection requests (cf. 21 CFR Part 812.140 – opens in a new window and 21 CFR Part 812.145 – opens in a new window)

For NC State IRB specific requirements for abbreviated IDE studies, please refer to the IRB unit standard on medical devices (Word document) and any relevant IRB guidance documents (see Appendix A for a short list of references).

For NC State IRB specific requirements for abbreviated IDE studies, please refer to the IRB unit standard on medical devices (Word document) and any relevant IRB guidance documents (see Appendix A for a short list of references).

An abbreviated IDE applies to research studying the safety and efficacy of a non-significant risk medical device. These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. The IRB serves as the FDA's surrogate for review,

approval, and continuing review of the NSR device studies. An NSR device study may start at the institution as soon as the IRB reviews and approves the study and without prior approval by FDA. There is no formal submission to the Food and Drug Administration (FDA) for a study evaluating the safety and/or effectiveness of an NSR device and there is no need to make progress reports or final reports to FDA.

Private IRB Review Request

Private IRB review will occur in very limited circumstances where the mobile software application or wearable that meets the definition of a medical device and the device is a significant risk device in need of an investigational device exemption (IDE). To date, the NC State IRB has not needed to send any study involving a mobile software application or wearable this is a medical device to a private IRB; if the need arises, however, the funded research project will be responsible for the costs associated with private IRB usage.

For more information, please review the IRB unit standard on the use of a private IRB (Word document) and, if relevant, the private IRB request form (Word document).

Device Types

Both mobile software applications and wearables, even if they do not meet the FDA's definition of a medical device, still have a "type" classification, which communicates who can access and use the product and what, if any, FDA regulation applies. There are three type classifications: commercially available, modified, and purpose-built.

Commercially available

Commercially available mobile software applications and wearables are devices that are accessible to the public to purchase legally through normal commercial channels. The research team uses the commercially available device with the research subjects without any modification. For applications and wearables that meet the FDA definition of a medical device due to their intended use in general not just in the research, the commercially available application or wearable is already cleared/approved by the FDA AND is currently being sold or marketed to consumers.

Modified

Modified mobile software applications and wearables are devices that are accessible to the public to purchase legally through normal commercial channels but prior to use in human subjects research the application or wearable has been changed in some manner. The change(s) could have been made by the research team or by a third-party, such as an Android application developer. Some examples of changes include changes to the software application's functioning itself or changes to how the software application communicates with a wearable such as a sensor or monitor.

For mobile software applications and wearables that meet the FDA definition of a medical device due to their intended use in general not just in the research, a risk determination (i.e., significant risk or non-significant risk) must be as part of the IRB review and approval process and by the FDA for significant risk devices.

Purpose-built
Purpose-built (sometimes called "homegrown") mobile software applications and wearables are those that are not available to the public to purchase legally through normal commercial channels. Purpose-built mobile software applications and wearables that meet the definition of a medical device due to their intended use in general not just in the research, require a determination of whether or not FDA regulations applies.

Mobile Medical Device
A mobile medical device is a portable device that is used for diagnosis of disease or other condition, treatment, or monitoring. Mobile medical devices may have hardware (sensors, electrical cabling), software, or connect to a mobile application or cloud to collect, share, or analyze data. Some examples of mobile medical devices are wearable heart rate or blood sugar monitors, electrocardiogram monitors.

The FDA provides a list of device software functions that the FDA regulates (opens in a new window) for a more detailed list of examples of mobile medical applications that would require FDA review. Researchers can search FDA's database of existing classification (opens in a new window) by type of mobile medical device to view a customized and more extensive list of devices that the FDA regulates to provide a better idea if FDA regulation might apply to your study.

What is and What is Not Regulated by the FDA

Mobile Applications Not Regulated As Medical Devices
A mobile application becomes a regulated medical device when it meets the federal definition in the FD&C Act of a medical device, i.e., intended use is to diagnose, treat, cure, or mitigate disease or other conditions in man or other animals or will change the structure or function of the body in a manner that is not chemical or through metabolization processes. The intended use can be inherent to the mobile application itself or can come about through the mobile application's use as an accessory to another regulated medical device or by combining the application with a device or operating software to function together in such a manner that meets the criteria of a regulated medical device*. To be clearer: When using a mobile software application with human subjects only as a tool, the FDA regulations most likely do not apply to the study. When, however, using a mobile software application as a medical device with human subjects and the application's safety or efficacy will be tested, the FDA regulations apply to the study.*

Mobile applications that are not considered medical devices under the FD&C Act are not regulated medical devices. There are six types of unregulated mobile applications: reference materials, education and training materials, general patient education, automations of general office operations in health care settings, and general-purpose products. All of these applications are not intended for use in the diagnosis of disease or other conditions, in the cure, treatment, mitigation, or prevention of disease, or to affect the structure or function of the body.

Reference Material

Mobile applications that provide electronic copies of medical textbooks and other reference materials with generic text search functions are functioning as reference materials. While the mobile applications that contain this material might assist a medical professional's clinical assessment of a specific patient, the mobile application is a tool that does not make a clinical assessment or judgement of a patient.

Some examples of mobile applications that function as reference material include:

- Medical dictionaries
- Digital copy of the *Physician's Desk Reference* (PDR) – a reference on drugs for health care providers
- Digital copy of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) – a reference tool for mental health care providers
- Library of clinical descriptions for diseases and conditions
- List of medical definitions and abbreviations
- Translations of medical terms across multiple languages

Educational and Training Material

Mobile applications intended for health care providers to reinforce their training or serve as an educational tool of medical training are serving as an education and training mobile application. These mobile applications typically have more functionality than applications functioning as reference material (e.g., interactive diagrams, videos) but, like reference material mobile applications, education and training materials applications are not regulated medical devices because the intended use is user education. The mobile application's education and training materials are not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease. The mobile application facilitates a health professional's assessment of a specific patient, but in no way replaces the judgment of clinical personnel or performs any clinical assessment.

Some examples of mobile applications functioning as education and training materials include:

- Quiz applications where questions and answers focus on medical education and training topics
- Flash care applications that include medical information, images, graphs
- Interactive anatomy diagrams or videos
- Surgical training videos
- Medical board certification or recertification preparation application
- Games that simulate various medical scenarios (assembling and operating ventilator equipment, cardiac arrest scenario) to build health professionals skills in advanced techniques (operating a ventilator under pressure, developing cardiopulmonary resuscitation (CPR) skills

General Patient Education Tools

Mobile applications that facilitate patient access to reference information for the purposes of awareness, education, and empowerment are not regulated medical devices because their intended use is to support patients, not for the diagnosis of disease or other conditions, or in the cure, treatment, mitigation, or prevention of disease by aiding clinical decision-making, replacing the judgement of a health care professional, or perform any clinical assessment.

Some examples of mobile applications functioning as general patient education tools are applications that:

- Compare costs of drugs and medical products at merchants in the user's location (e.g., GoodRx)
- List the closest doctors and medical facilities to the user that accept the user's health insurance
- Provide lists of emergency and medical advice hotline phone numbers
- Healthcare providers use to distribute educational information (e.g., interactive diagrams, relevant links or resources) to patients regarding their disease, condition, treatment, or upcoming procedure
- Guide patients to ask appropriate questions to their health care provider

- Match individuals to potentially appropriate clinical trials and facilitate communication between potential participants and researchers

- Provide tutorials or training videos on how to administer first aid or cardio-pulmonary respiration (CPR)

- Scans pill color, shape, imprint, and displays pictures and names of pill that match the scanned data (e.g., WebMD's Pill Identifier)

- List food allergy-friendly food products or restaurants

- Provide digital education tools, quizzes, games, and questionnaires that help engage patients to actively participate in their general health and wellness (calorie consumption, benefits of physical activity)

Automations of General Office Operations in Health Care Settings

Mobile applications that automate general office operations in health care settings are not regulated medical devices so long as they are not intended for use in the diagnosis of disease or other conditions, or in the cure, treatment, mitigation, or prevention of disease.

Examples of mobile applications that automate general office operations in health care settings include applications that:

- Utilize published resources such as The International Classification of Diseases, Tenth Edition (ICD-10) and assign codes to medical procedures for the purposes of billing health insurance companies

- Collect data for the purposes of processing health insurance claims or to analyze insurance claims for fraud or abuse

- Track hours worked for workload trends, billable hours, and volume of types of procedures conducted

- Help patients track, review, and pay medical claims and bills online

- Generate appointment reminders

- Manage staffing schedules of medical providers

- Manage or schedule occupancy rates of hospital beds or patient rooms

- Provide electronic check-in and estimated wait times for medical care facilities such as urgent care

- Healthcare providers or staff use to process payments for services rendered or visit co-payments

General Purpose Aids and Products

Mobile applications that function as general aids or for a general purpose are not regulated medical devices because they are not intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals.

Some examples of mobile applications that function as general aids or general-purpose products include applications with:

- Magnifying and flashlight function for general (non-medical) use, such as illuminating and zooming in on a small surface area for home repair or crafting purposes
- Audio/video recording, transcription, and replay functions for general (non-medical) use, such as documenting parent-teacher conference meetings
- Speakerphone function for general (non-medical) use, such as to include multiple people in one room on a phone call
- Live translation function for the purpose of clear speech
- Platforms that facilitate digital communication between parties for purposes other than medical care or treatment
- Maps and turn-by-turn navigation for general use

Mobile Applications Regulated as Medical Devices

Mobile applications that do meet the definition of a medical device in the FD&C Act can either be subject to regulation at the FDA's discretion or via active regulation. A detailed exploration of the regulatory levels, requirements, rationale, and lists of mobile application types regulated as medical devices can be found in the FDA's Policy for Device Software Functions and Mobile Medical Applications Guidance for Industry and FDA Staff (PDF file), but to summarize, there are three types of regulation: actively regulated, subject to the FDA's discretionary enforcement, and exempt from FDA regulation.

Actively Regulated by the FDA

Mobile applications are subject to active FDA regulation if they meet the definition of a medical device, have a risk level that is greater than "low risk," and:

1. Connect to an existing medical device (e.g., blood pressure cuff, blood glucose monitor) for the purposes of controlling its operation, function, or energy source;

2. Display, transfer, store, or convert patient specific medical data from a connected medical device;

3. Transform a mobile platform into a regulated medical device through a software function; or

4. Perform patient-specific analysis and provide patient-specific diagnosis or treatment recommendations.

Some examples of mobile applications that meet the FD&C Act's definition of a medical device, the FDA identified as subject to active regulation, and are particularly relevant to current NC State University research enterprise interests include applications, software, or devices that:

- Measure blood oxygen saturation
- Collect or measure physiological data (e.g., limb movement, electrical activity of the brain (EEG))
- Measure and display the electrical signal produced by the heart (i.e., electrocardiograph (ECG))
- Record, view, or analyze eye movements
- Use a microphone or speaker as an audiometer to determine hearing loss
- Remove hair
- Treat skin conditions
- Electronically amplify and "project sounds associated with the heart, arteries and veins and other internal organs" (i.e., an electronic stethoscope)

This is not an exhaustive list. NC State University researchers are expected to keep abreast of FDA's expectations.

Subject to FDA's Discretionary Enforcement

Mobile applications are subjectively regulated by the FDA if they meet the FD&C Act's definition of a medical device but their use is considered *by the FDA* to be low risk.

Some examples of mobile applications that meet the FD&C Act's definition of a medical device, the FDA identified as subjectively regulated, and are particularly relevant to current NC State University research enterprise interests include applications, software, or devices include those that:

- Log, track, and trend data such as blood glucose, blood pressure, heart rate, weight, personal health incidents, or other data from a device that users can share with others (e.g., a healthcare provider) or upload to an online (cloud) database, personal or electronic health record

- Individuals use to log, record, track, evaluate, or make decisions or behavioral suggestions intended for developing or maintaining general fitness, health or wellness, such as those that:

    - Provide dietary logs, calorie counters or make dietary suggestions

    - Provide meal planners and recipes

    - Track general daily activities or make exercise or posture suggestions

    - Actively monitor and trend physical activity

    - Calculate calories burned in a workout

    - Help healthy people track their sleep quantity or quality patterns

    - Track a normal baby's sleeping and feeding habits

    - Provide and track scores from mind-challenging games or generic "brain age" tests

    - Provide daily motivational tips (e.g., via text or other types of messaging) to reduce stress and promote a positive mental outlook

    - Use social gaming to encourage healthy lifestyle habits

- Use GPS location information to alert asthmatics of environmental conditions that may cause asthma symptoms near a pre-identified, high-risk location.

- Help asthmatics track inhaler usage, asthma episodes experienced, location of user at the time of an attack, or environmental triggers of asthma attacks.

- Display, at opportune times, images or other messages for an addict who wants to stop their consumption of habit-forming substances.

- Help individuals with diagnosed psychiatric conditions (e.g., post-traumatic stress disorder (PTSD), depression, anxiety, obsessive compulsive disorder) maintain their behavioral coping skills by providing a "Skill of the Day" behavioral technique or audio messages that the user can access when experiencing increased anxiety.

- Prompt user to manually enter symptomatic, behavioral or environmental information pre-defined by a healthcare provider and store the information for later review

- Provide patient-specific screening, counseling and preventive recommendations from well-known and established authorities by using provided demographic data such as age, sex, and behavioral risk factors

- Provide a surgeon with a list of recommended equipment and surgical approaches based on data inputted by surgeon

The above list of mobile applications that are subjectively regulated by the FDA is not exhaustive. In addition to those examples, remember that the FDA's medical device regulations generally don't apply if the research team uses an FDA approved medical device to:

- collect physiological data but no data is collected about the device;

- address a research question but no data is collected about the device; or

- implement a clinical investigation if *there is no intent to collect safety or efficacy data about the mobile application or to develop the mobile application (software, hardware, device) for marketing.*

Exempt from Pre-Market Notification Requirements

Some medical devices are exempt from pre-market notification requirements by the FDA. This is because use of the medical device is considered low risk and the medical device is considered "substantially equivalent" to devices already on the market. A few examples of "substantially equivalent" devices include manual wheelchairs, elastic bandages, tongue depressors, mercury-free thermometers, and non-prescription eyeglass frames.

Even if the FDA doesn't require pre-market notification for a medical device, the device itself must be registered, listed, and labeled with specific information. There must also be specific record keeping processes with measures for monitoring, quality assurance, and handling of problems with the device itself or how it is used. A study can be exempt from the PMR notification, but not from the

FDA's regulatory oversight of a medical device in research via an IDE application as IDEs apply to clinical research and PMRs and 510Ks are pathways to marketing.

For medical devices exempt from FDA regulation, the risk assessment is made by the FDA through its exemption qualification criteria.

Please note that exemption from the FDA regulation does not mean that the medical device is exempt from IRB review or qualifies for an exemption determination from the IRB office.

Wearables Not Regulated as Medical Devices

Wearables are standalone technology that detects and/or captures physiological data. Some wearables include or connect to software (e.g., Garmin Connect, Apple Fitness+) or external hardware (e.g., skin sensors) to collect or capture the physiological data. The hardware may be novel, but unless the wearable or connected hardware or software is intended to diagnose disease or other condition, or treat, mitigate, cure disease, or affect the structure or function of the body, then the wearable is not regulated as a medical device

Some examples of wearables that are not regulated as medical devices include:

- Fitness bands tracking steps, activity, heart rate, sleep intended for general wellness
- Smartwatch functions tracking physical activity intended for general wellness
- Smart glasses for altered/virtual reality or recording intended for entertainment
- Smart clothing that tracks physical movement for performance data
- Wearable headbands (e.g., Muse), wristlets, or rings (e.g., Oura Ring) that track surface tension or temperature to encourage wellness habits such as meditation, hydration, and physical activity
- Wearable cameras, such as GoPro, intended for documentation or entertainment

Wearables Regulated as Medical Devices

Wearables are only regulated when they meet the definition in the FD&C Act of a medical device, which focuses on the intended use of the wearable. If the wearable is intended to diagnose a disease or other conditions, or to treat, mitigate, or cure disease, or to change the structure or function of the body (human or other animals), then it is a medical device. Intended use is key –a wearable that asserts specific health claims in regard to its intended use, such as "detects Afib" is intended to be used as a medical device.

Some examples of wearables and their name brands that are regulated as medical devices include:

- Biosensors that track body temperature, respiratory rate, heart rate – BioButton (opens in a new window)
- Continuous blood pressure monitoring wearable – Omron HeartGuide (opens in a new window)
- Continuous heart rhythm monitoring patch - ZioPatch (opens in a new window)
- Continuous glucose monitor (CGM) - Dexcom (opens in a new window), FreeStyle Libre (opens in a new window)
- Electroencephalography (EEG) headset or fingertip monitor for brain activity – KardiaMobile (opens in a new window)
- Seizure detection wearable – Empatica Embrace 2 (opens in a new window)
- Smart ring or band that detect falls or send medical alerts, depending on what the intended use is - Invisawear (opens in a new window)
- Smartwatch functions that track the electrical activity of the heart muscle (i.e., electrocardiogram (ECG) function) – Apple Watch (opens in a new window), FitBit Sense 2 (opens in a new window), Samsung Galaxy (opens in a new window)

It's important to remember that with wearables, the sensors used in wearables are usually novel without a predicate device that the sensors are linked to. This means that if the sensors are being tested for safety or efficacy or for data that a research team would want to use for an FDA marketing license in the future, then after IRB processes involving an abbreviated IDE determination, FDA processes such as a 501(k) clearance application (opens in a new window) for Class II devices or a premarket approval (PMA) (opens in a new window) process with the FDA for Class III devices may apply. Any use of the sensors with human subjects would require IRB review and approval by the convened full board who would also need to grant an abbreviated IDE for the sensors.

Uses in Human Subjects Research

Mobile software applications and wearables determined to be medical devices can be used in human subjects research in several ways:

"On label use"

On label use is when a software application or wearable that meets the FDA's definition of a medical device is used in the manner it is intended to be used with the population(s) and setting(s) that it's intended to be used by, and with the established conditions of use established by the FDA's labeling.

"Off label use"
Off label use is when a software application or wearable that meets the FDA's definition of a medical device is used for a purpose, in practice(s) or setting(s), or with a population that the FDA has not approved. This means that even if the software application or wearable is approved by the FDA but its use in research is with a different population or for a different use than what the FDA approved, the use is "off label."

There is some flexibility in FDA processes for individuals who are licensed health care clinicians to justify "off label" use of a software application or wearable by documenting rationale for use and obtaining participant consent. Researchers, software developers, and wearable manufacturers, however, are expected to proactively comply with all FDA processes applicable for research and investigational use of mobile software applications and wearables that meet the FDA's definition of medical devices. Those with dual roles as health care clinicians and researchers should comply with the more restrictive FDA expectations for researchers.

Combination use with one or more medical device(s)
The combination use of a software application or a wearable with a medical device, known as "combination use," can make the software application or wearable a medical device if the combination use supports an "intended use" that meets the FDA's definition of a medical device. Additionally, if combining the software application or wearable to a medical device changes the performance (e.g., functioning) or use (e.g., drives medical decision-making) of the medical device, the entire combination might be considered a medical device regulated by the FDA even if the software application or wearable on its own is not regulated by the FDA.

A few examples of a combination medical device include:

- A smart ring (e.g., Oura) that does not make any claims to diagnose, treat, cure, or mitigate disease is a general wellness device, but if that data is inputted into an electronic health record (EHR) that then diagnoses "early COVID-19 symptoms" – the ring in combination with the EHR is a combination device subject to FDA regulation.

- A fall harness on its own is a regulated medical device because its intended use is to prevent injury, but it can also become a combination device when paired with a sensor or application software to record biometric data (heart rate, oxygen saturation), detect a fall, alert caregivers/first responders, or suggest treatment (e.g., injury assessment recommendation)

- An electrocardiogram (ECG) function wearable such as a smartwatch is a FDA-regulated medical device on its own due to the ECG. If it is paired with an artificial intelligence (AI) algorithm to predict stroke risk, the combination is functioning as a diagnostic tool that is either “off label” use or a new medical device subject to FDA regulation depending on the particulars of the wearable and algorithm.

- A continuous glucose monitor (CGM) paired with a software application that tells a user how much insulin to take is a regulated medical device because the CGM data sent to the software application is used to recommend treatment of a disease (diabetes) so the combination is regulated by the FDA.

Used as a data collection tool

Mobile software applications and wearables can be used as data collection tools in human subjects research. The intended use of the technology and how the data generated from the software application or wearable is used, will determine whether FDA regulation will apply. In general, if the software application or wearable’s intended use is data collection and not also making specific claims about disease or other conditions, being used for diagnosis, treatment, mitigation, or cure of disease, or tested for safety or efficacy claims, then the usage of the software application or wearable in the research study is likely not FDA regulated.

For example, if a research study asks participants to wear Fitbits to track heart rate and sleep cycles, step on a scale and weigh themselves once a week at home, and track what they eat each day in MyFitnessPal software application and all of this data is shared directly with the research team for the sole purpose of data analysis, the intended use of the Fitbit, scale, and calorie counting application are general wellness devices. The software application (MyFitnessPal), scale, and the wearable (Fitbit) are functioning in this study as data collection tools, not medical devices, because at no point is the software application or wearable making health claims about the participant or being used for the purposes of healthcare decision-making. They are data collection tools only.

If, however, any of the following was added to the research design such as:

- the FitBit data shared with the research team included electrocardiogram (ECG) data; OR

- the weight scale is used in conjunction with a wheelchair, hospital bed, is integrated with an individual’s electronic health record, or guides treatment of a medical condition; OR

- the calorie counting application develops a personalized diet to treat an eating disorder, is used in conjunction with weight loss medication to monitor individual's health condition, or recommends calorie deficit to reverse a health condition

then any of those uses would be subject to FDA regulation because the use is more than just data collection and the use informs the diagnosis or treatment of disease. Please note that IRB's scope of practice focuses on the medical device's use with human research subjects. FDA processes related to regulation, labeling, marketing, and approvals are separate from IRB processes.

Usability testing

Usability testing of a software application or wearable is when the research team focuses on how the participant interacts with the item to assess if the software application or wearable is operable without error by device or user and that its communications to user (e.g., use instructions, visual layouts, push alerts, etc.) are clear and accurate. Usability testing is also called "human factors" testing.

Usability testing is a key element of developing medical devices, including mobile software applications and wearables functioning independently as a medical device or are a medical device because they are intended for use in combination with one or more items that is intended for use as a medical device. The FDA requires usability testing for most Class II and Class III devices and for medical devices that are novel. Components of usability testing include:

- User analysis to define who will use the medical device
- Task analysis to determine how the medical device will be used
- Environmental analysis to define when and where the medical device will be used
- Prototype testing to refine usability
- Validation testing to ensure that the medical device is usable with the population(s), context(s), and purpose(s) it is intended for
- Root cause analysis to address any use issues to improve design and operation of the medical device

If you plan to do usability testing, we strongly recommends that you review the IRB unit standards and guidance listed in Appendix A, especially on pilot studies and feasibility work, phased and staged research, medical devices, as well as reviewing all FDA guidance on human factors and medical devices (opens in a new window). Usability testing usually requires IRB approval.

Safety and/or efficacy testing

Safety and/or efficacy testing is when a software application or wearable that meets the FDA's definition of a medical device on its own or in combination with other item(s) is evaluated to see if it causes harm (i.e., safety testing) and/or works as intended for the purpose the medical device is intended for (e.g., efficacy testing). Whenever a medical device is being tested for safety and efficacy, the research study requires IRB review and approval including a non-significant risk/significant risk (NSR/SR) device determination. The NSR/SR device determination informs whether the research team is required to apply the FDA for an Investigational Device Exemption (IDE) or to the NC State University convened full board for an abbreviated Investigational Device Exemption (abbreviated IDE).

Components of safety and/or efficacy testing can include:

- Functional validation that the medical device works in the manner intended for the purpose intended
- Clinical validation that the medical device accurately measures what it's supposed to.
- Safety testing that there are checkpoints and endpoints for medical device usage that reduce or eliminate potential harm(s) of medical device usage
- Usability testing that users can operate the medical device without error that causes harm to users or inaccurate data collection

There are several stages of safety and efficacy testing, which are:

1. Bench testing is the first step in safety and efficacy testing where a prototype software application or wearable is developed and its performance is tested WITHOUT any human research participants (this includes the inventor, principal investigator, and members of the research team). The bench testing focuses on design, function, and use applications of the software or wearable to develop a prototype.

   Bench testing can present as:

   - testing a skin sensor's calibration is accurate
   - testing that a wearable and software application could work together
   - testing that all data transmissions between devices and networks are accurate, etc.

2. Preclinical data stage follows bench testing. It can include secondary data as well as primary data collection where one or more human participants test the software application or wearable for usability, performance, safety (especially with wearables that can cause shocks/burns), risks, data accuracy, and data security. The purpose of the preclinical data is to identify issues before clinically testing the software application or wearable by validating its design, managing risks in the design, and start collection of information that will support claims of safety and effectiveness to the FDA.

   Some examples of preclinical data collection are looking at:

   - if a wearable won't irritate the human body part its designed to be worn on
   - if a mobile software application functions well with all of the devices its connected to during use
   - if the data collected/used by the mobile software application or wearable is accurate

3. Clinical data builds upon preclinical data by further testing a mobile software application or wearable with a larger group of human participants. Often facilitated through the implementation of clinical trials where participants are prospectively assigned to an intervention group, which can be a control group, the software application or wearable is tested in real-time for safety and efficacy data, usually though several data collection phases and modes. This requires both IRB approval and application of the FDA's IDE requirements. At NC State, most clinical data studies receive an abbreviated IDE determination during the IRB convened full board review process because the medical device being studied is determined by the convened board to be a non-significant risk device.

   Some examples of clinical data collection are:

   - comparing the data from an ECG (electrocardiogram) done by a healthcare provider to an ECG reading from a wearable to see if the data is comparable and equally accurate
   - testing a wearable's ability to detect and report a user's falls accurately by having participants intentionally fall in a lab visit while wearing the device and having participants in elder care housing who are prone to falls also wear the wearable

- testing the electrode accuracy on a wearable headset to see if it can accurately detect and track a user's brain seizure activity

- testing whether an artificial intelligence (AI) tool can accurately diagnose and recommend contextually appropriate treatments at the same success rate as licensed and actively practicing oncologists

4. Post-approval monitoring from the FDA occurs after the mobile software application or wearable that meets the FDA's definition of a medical device has been cleared or approved by the FDA. The medical device is available to the public at this phase, but continuous data collection and monitoring is ongoing to ensure that the initial claims about safety and efficacy of the device are supported with a broader user pool. Post-approval monitoring is required for all Class III medical devices, usually done (sometimes required, sometimes voluntary) for Class II devices, and rarely done for Class I devices.

Defining Research

Before discussing different research types and expectations, it is critical to acknowledge that by using a mobile software application or wearable that meets the FDA's definition of a medical device means operating under two different sets of federal regulations, each of which has its own (i.e., different) definition of research.

Under the IRB regulations called the revised Common Rule (45 CFR 46) (opens in a new window), research is something that is both "systematic" and "designed to develop or contribute to generalizable knowledge" or has the intention of doing so.

The Food, Drug, and Cosmetic Act (FD&C Act) [21 CFR 56.102(c)] (opens in a new window)'s regulation defines research more broadly as a "experiment that involves a test article and one or more human subjects." ***Even if the investigation is not systematic or designed to develop or contribute to generalizable knowledge, if a medical device is involved with one or more humans and the intention of the experiment is to generate data that will be later submitted to the Food & Drug Administration to support an application for research or marketing of the medical device, than the work is, by U.S. Federal law, research***.

The NC State IRB always follows the rule of the most restrictive, which means in practice that if a study meets one or both federal definitions of research provided in the revised Common Rule or the FD&C Act, it is subject to IRB review if the work also meets the definition of human subjects research of involving living humans, the research is "about" the human (e.g., their demographics, behavior patterns, biological processes or specimens, beliefs or preferences, etc.), and the data is collected through interaction, intervention, manipulation of environment, or personally identifiable private data.

The NC State IRB's Expectations for Different Research Types
Beyond the general IRB review and approval requirements for all human subjects research proposed to the NC State IRB office, there are additional expectations and requirements for specific research types listed below.

Phased and Staged Research
Phased and staged research occurs in sequential steps with each step having its own research question(s). It is a common format for clinical trials that investigate a health-related outcome, either biomedical or behavioral. The first step of phased research for mobile software applications and wearables medical devices can include prototyping, simulated use, and small pilot studies. Later steps in phased research expand to investigating the device in real world settings, with more users, and ongoing safety, efficacy, usability, and risk assessments and data collection.

IRB review is required for all phased and staged research involving one or more humans that meet the definitions of research (45 CFR 46 (opens in a new window) or 21 CFR Parts 50, 56, 312, and/or 812 (opens in a new window)) and human subjects research even if the human on whom the mobile software application or wearable will be used is a part of the research team or if the research purposes is for usability. This includes pilot studies where the only human subject involved in the phase is the principal investigator or a member of the research team.

When applying for phased and staged research, the IRB application must provide all materials seeking IRB review and approval at the time. Future protocol amendments will detail later phases and provide supporting documentation for those new procedures. Researchers should not apply for IRB approval for all phases of a staged research study if their materials are not ready for final review.

To apply for phased research, review the phased and staged research guidance (Word document) and, if applicable, the guidance on applying for a .118 determination (opens in a new window) for NSF funded research or the Just-in-Time guidance (Word document) for NIH funded research – both which are not yet conceptualized and ready for IRB review.

Clinical Trials
Clinical trials are a type of phased research study that prospectively assigns one or more humans to a research intervention for the purposes of studying a health-related outcome. A research intervention can be a control arm of a study just as it can be an intervention from the research team, while the health-related outcome can be biomedical or behavioral in nature.

All clinical trials will have primary and secondary endpoints for the study. It is expected that primary endpoints will include those related to safety or efficacy of the mobile software application or wearable as a medical device *even if that is*

not the intended purpose of the study's data collection. All endpoints must be articulated in the IRB application and, as appropriate, in the participant consent materials.

There are additional regulatory requirements for all clinical trials, including those using wearables and mobile software applications, such as registering the study with http://www.clinicaltrials.gov, publicly posting consent materials, and providing annual updates as well as final study results to the public. More information about the requirements for clinical trials can be found in the NC State IRB unit standard on clinical trials (Word document).

Human Body Movement and Characteristics Research

Human body movement and characteristics research at NC State University can take the form of exercise science, garment testing, body scanning, and biomedical engineering prototyping and testing. Some of the unique concerns and regulatory requirements that pertain to these types of research include:

- If asking participants to provide maximum physical effort on their own or through the use of a medical device such as a BioDex, the likelihood of injury is more than minimal risk and the study must be reviewed by the convened full board even if the exercise equipment itself could be classified as general wellness items. With maximum effort exercise, it is expected that muscle soreness and injury will be study risks that must be articulated and addressed in the IRB application and supporting documentation files such as the consent form.

- When participants will be asked to wear items, the IRB needs to know how the item will be donned and doffed, where on the body the item(s) will be worn, who will place the item (participant themselves or a member of the research team), as well as what complications might occur. For example, skin sensors that attach to the skin via adhesive could irritate or tear skin and those that are wired could be a tangle/trip/fall hazard depending on where the skin sensor is placed and what body movement the participant will be engaged in. Likewise, if a participant could fall while engaging in physical exercise (e.g., treadmill walk/run, force plate jumping, carrying weights while walking with a power-assist prosthetic leg), the IRB expects that precautions such as the use of a fall harness is employed. In addition to use within the study, participants must be given a private location to undress and re-dress if clothing changes are necessary for study procedures.

- If a wearable will be used, indicate both in the IRB application and the consent materials any exclusion criteria, such as 40" maximum waist to fit the fall harness, individuals who wear glasses cannot wear the eye tracking headset, individuals with a history of seizures cannot participate due to the device potentially triggering seizure activity, etc.

- Some studies test textiles or garments in controlled environments that subject participants to environmental stressors such as wintergreen oil and high heat and humidity The IRB expects that in these cases that precautions will be taken to protect participants from the environmental stressors by providing, as applicable, hydration and hydration cues, anti-itch or skin irritation cream, respiratory equipment, and use of a core body temperature pill if it is likely that a participant might overheat during research procedures. When a wearable such as a core temperature pill will be used, the research team must upload an information sheet for the IRB to review that will be provided to participants that explains in lay language what the core temperature pill is, how it works, why it's being used in the study, instructions on how to use it, what the complications of use might be, and when to seek medical attention.

- If a study will be testing a prototype wearable that will hold a medical device, such as a hoodie that is designed to hold wearable sensor device to monitor geriatric pregnancy health of parent and fetus, the IRB application must discuss in detail what the risks and benefits of the study might be for both the person pregnant and the fetus as well as whether the prototype garment will have any impact upon the device's functioning in addition to all of the normal medical device information.

- If a study will be testing a wearable that has carcinogenic properties or dyes (i.e., regulated by the FDA), that must be disclosed to the participant in the consent materials as well as in the IRB application along with the steps the research team will take to mitigate these risks such as an additional clothing layer between the skin and the wearable.

- Some studies testing a wearable might ask participants to shave a particular body part. Detailed procedures must be outlined in the IRB application, including what body parts and who will be doing the shaving of the body part(s). Shaving procedures must be mentioned in the consent form.

- Some studies testing a mobile software application or wearable need to collect sweat to test the safety or efficacy of the medical device. Studies that have participants engage in physical exercise to noninvasively provide sweat are far less risky than using venipuncture to obtain human sweat. If the riskier procedure has been chosen, the research team must provide justification for why a less risky alternative would not be feasible to provide the data they need to answer the research question.

- When a study needs to collect brain activity data, the IRB expects that the IRB application will discuss how the participants will prepare for those procedures, specify what inclusion/exclusion criteria will be used for the

type of medical device and gel used, and what aftercare instructions will be given to participants. This content should also be reflected in the participant facing materials such as the consent and participant communications materials.

- Some studies will ask a participant to have their body scanned or be weighed. The NC State IRB expects that participants with disordered eating or a history of it will be excluded. Participants must also be informed how the body scan will be conducted (i.e., Clothed? Unclothed?), what will be recorded, and if the data will be recorded in an identifiable manner or in a manner where the body would seem to be "nude" instead of clothed.

- If a participant will be downloading a mobile software application to their own personal device, an information sheet(s)for participants with instructions on how to access, download, and safely use the mobile software application must be provided – for further instructions, please consult the IRB guidance on applications and software (Word document), IRB guidance on artificial intelligence (Word document) if applicable, and the IRB unit standard on medical devices (Word document).

- If a study will be recording participants, what platforms that will record the participants and where those recordings will be saved must be articulated in the IRB application. The NC State IRB does not endorse saving any research recordings to a cloud, favoring instead local recordings on NC State managed devices wherever possible. For more information, please review the NC State IRB's guidance on images and recording in human subjects research (Word document).

Big Data and Data Scraping Research

When pulling data from mobile application software platforms or a wearable, if the data is not generated for the study, it is considered secondary data research for which the research team should review the guidance on secondary data and the IRB (Word document) and, if applicable, the IRB's unit standard on FERPA (Word document), unit standard on HIPAA (Word document), and guidance on artificial intelligence (Word document).

The IRB's chief concerns with this type of research is:

- How the research team will gain access to the data – that is, just because you can doesn't mean you should. There can be additional privacy laws that apply to secondary data research. Participant consent ideally will always be sought and in some cases may be legally required for accessing such data for research purposes even if one already has access to the data due to their role (e.g., University faculty, medical provider, etc.)

- All secondary data that will be inputted into a modified or purpose-built mobile software application must have a code review conducted by an subject matter expert (SME) who is not a member of the research team, the project's sponsor/funder, and does not stand to benefit from the results of the research. A completed code review form (Word document) must be uploaded to the IRB protocol's supporting documents prior to final review.

- Sourcing data via GitHub is allowable if articulated in the IRB application, but the research team cannot use any language with participants as part of the consent to research that is exculpatory (that's fancy language for threatening) in nature or induces panic in participants by telling them their data has been robbed and their consent will help "protect" their data.

- When conducting big data research, the IRB is concerned about the identifiability of participants via their data and who besides the research team will have ancillary access to the data. That is why for this type of research in particular, the IRB looks very closely at the data management plans articulated in the IRB application.

Software, Hardware, Device Development Research

When a medical device's software or hardware is being developed with human subjects use and feedback, the research can go in a number of directions and steps such as phase 1 prototyping, phase 2 pilot study, phase 3 main study, etc. Refer to the above sections on phased research, but for software and hardware that are part of medical device development in particular, the IRB application must:

1. Justify use of any modified or purpose-built hardware or software in the wearable or mobile software application over a commercially available and unmodified product.

2. Explain what the purpose of using the software/hardware is and the risks to participants and their privacy if the item is used with them or their data.

3. Provide a completed code review form (Word document) to the IRB as part of final review of the modified or purpose-built component functioning as a medical device.

4. Provide a completed medical device used in research form (Word document) for each software, hardware, or device that will be used in the study with participants and/or their identifiable data.

5. Provide information sheet(s) (Word document) for participants with instructions on how to access, download (if applicable), and safely use the mobile software application or hardware if they will be using the item

outside of a lab or on the participant's personal device instead of an NC State managed one.

6. Researcher personal device use attestation (Word document) if applicable.

7. Application software informed consent addendum (Word document) if applicable.

8. Completed a completed code review form (Word document) for each modified or purpose-built mobile software application or wearable(s) that include digital component(s).

9. HIPAA participant authorization and revocation form (Word document) or request to waive participant authorization form (Word document), if applicable to the study.

Veterinary Science Research

In the veterinary field, there can be a lot of work that while it is focused on non-human animals can also be human subjects research. For a thorough discussion of what is human subjects research and necessitates an IRB application, veterinary researchers should review the IRB guidance for the College of Veterinary Medicine (Word document).

Human-animal research with mobile software applications or wearables can include things like:

- Mobile applications that track food intake, litter box use, and survey owners about their pet's habits

- Personal flotation equipment (PFEs) for humans and non-human animals

- Data scraping from mobile software applications to collect data about the human and their pet from items purchased, frequency of physical exercise, etc.

There also can be studies where a mobile software application, wearable, or drug is approved by the FDA for use in non-human animals but it is not approved for use with humans. An example of this would be use of a topical cream on a canine. In a clinical setting, it's fine for the veterinarian to use but if non-professionals such as owners are asked to apply it to their dog as the cream is a drug regulated by the FDA and only approved for topical use with canines not humans. In those cases, the IRB will work with the research team to identify how to satisfy FDA regulatory requirements which will be specific to the medical device or drug that will be used in the study and how it will be used in the study. In another example, a medical device of a surgical drape is approved for use with

the non-human animal to prevent unintentional radiation exposure but the drape is not approved by the FDA to be used on humans for the same purpose of limiting radiation exposure. Again, the regulatory requirements for the study will depend on the nature of the medical device and how it is being used in the study.

Use of Artificial Intelligence and Generative Artificial Intelligence
Research with artificial intelligence (AI) and generative artificial intelligence (GAI) is a rapidly evolving area of research in general as well as in mobile software applications and wearables. Researchers are encouraged to review and bookmark the IRB guidance on artificial intelligence and generative artificial intelligence in human subjects research (Word document) for an in depth discussing of the issues and requirements that the IRB has for the use of AI and GAI in research.

AI and GAI is being used to facilitate research processes with participants, interact with participants through mobile software applications and wearables, and analyze participant data. Where the NC State IRB is particularly concerned about the use of AI or GAI is when its use drives decision-making in research including research conclusions and how model drift is monitored and corrected.

In addition to referring to the IRB guidance on artificial intelligence, the below links can also be helpful in designing this type of research:

1. A basic overview of How the FDA regulates AI in Medical Products (opens in a new window)

2. Published list of AI Enabled Medical Devices (opens in a new window)

3. Good Machine Learning Practice for Medical Device Development: Guiding Principles (opens in a new window).

Ambient Recording
While the NC State IRB has published guidance on images and recording in research, there are particular risks that come with mobile software applications or wearables that record data that might be subject to unintended consequences. For example, a study records a person's sleep activity including sound recording to capture snoring or apnea. The sound recording also captures other nightly activities of individuals in the recording area, some of which are private intimate activities, and the individuals involved may or may not have consented to research. Likewise, recorded activities may come with mandatory reporting responsibilities such as a participant who has a wearable camera on their chest recorded waving a gun at other people in a threatening manner. It is permissible to record participants for research purposes with their consent, but the NC State IRB will insist that the research team provide participants with direct, succinct information in lay language about what will be recorded, what risks (personal

privacy and otherwise) there are in terms of what is recorded, and what mandatory reporting responsibilities the research team has.

Levels of IRB Review

Mobile software applications functioning as a medical device span a wide range of health functions. While many mobile applications carry minimal risk, mobile medical apps that can pose a greater risk to patients/users will sometimes require FDA review for a risk determination (significant risk vs. non-significant risk) and/or an investigational device exemption (IDE). The level of IRB review for human subjects research with the mobile software application that is a medical device will depend on several factors: if the mobile software application as a medical device is already cleared or approved by the FDA and will be used on label for the purpose and population(s) that the FDA cleared/approved its use with, what device classification level the mobile software application is (Class I, II, or III), what the mobile software application's risk determination is (nonsignificant risk devices can be reviewed at the expedited level *if all other components meet the criteria for mid-level IRB review*, but significant risk devices can only be reviewed at the convened full board level), and what the mobile software application as a medical device does (informing care is one thing, driving care is another, more risk position).

Most wearables that qualify as medical devices aren't yet approved by the FDA OR aren't commercialized and adopted for clinical decision making. Happily, though, most wearables research is usage as a research tool (eligible for expedited review) or are proof-of concept prototypes (e.g. a simple version to test feasibility of future development) that need humans to test it before the safety/efficacy of the medical device is assessed. As a result, wearables are often eligible for expedited review.

Expedited Review

Expedited review occurs if a mobile software application or wearable that meets the definition of a medical device and is FDA cleared or approved and used for its intended purpose and user population OR the device is being used as a data collection tool only and no safety or efficacy data is being collected. Regardless of expedited category, the study must be minimal risk to participants and the device must be a nonsignificant risk (NSR) device per the FDA's established criteria.

The expedited categories of IRB review (opens in a new window) that a mobile software application or wearable that is a medical device might fit into are:

Category 1: Clinical investigation of a drug or device

This is where the mobile software application or wearable is already cleared (via 501(k)) or approved (via PMA) by the FDA for marketing and used within the FDA-approved scope OR the device is diagnostic but the research does not require either an abbreviated IDE or an IDE from the FDA because the device itself is noninvasive, its use doesn't require any invasive sampling, it doesn't introduce energy into the body, and it's not

used diagnostically without confirmation by a separate evidence-based, best practice mean.

Category 3: Biospecimens collected non-invasively
This category is for wearables that may collect biospecimens for research purposes, such as human saliva from a nasal cannula, human excrement from an adult diaper, continuous glucose monitors that collect blood to document blood sugar levels, an absorbent headband that collects sweat to monitor a user's electrolyte balance and hydration, lactate monitors that collect sweat to assess lactate byproducts to infer exercise intensity, fatigue, and oxygen levels. Depending on the design and function, a biosensor may or may not fit into category 3.

Category 4: Collection of data non-invasively
This category is used a lot at NC State University because it allows passive and active data collection for medical devices such as weight scales, tape measures, eye trackers, heart rate monitors, smartwatches, etc. The key is that the medical device in this category either have to be cleared or approved by the FDA and used within scope OR the device is not be approved by the FDA but the device is only being used as a tool, the research is minimal risk, the device is nonsignificant risk (NSR), and the research is not collecting any data on the device's safety or efficacy. This is greater flexibility than in category 1, where the device needs to be cleared or approved by the FDA. In this category, even if the device is cleared or approved by the FDA and used on label, the device cannot introduce energy into the body. Thus, x-rays and (sometimes) body scanning procedures cannot fit into category 4 research.

Category 5: Secondary data
This category covers data that is either collected for a non-research purpose (e.g., big data scraping) or for research purposes (e.g., a study asks participants to use specific mobile software application(s) or wearable(s) as part of the study). This category can include data that is subject to FERPA and/or to HIPAA – where the secondary data is analyzed by software in a medical (SiMD) device or as a medical device (SaMD) to improve or design new mobile software applications or wearables, predictively models problems or behavior to assist device testing, or used to diagnose a disease or other condition.

Category 7: Individual or group characteristics or behavior
This category includes a lot of mobile software applications and wearables research at NC State University such as devices undergoing prototyping, usability testing, therapeutic interventions, participant interventions, etc. – as long as the device itself is not being tested for safety or efficacy.

We also recommend that you review the NC State IRB's unit standard on expedited review procedures (Word document) for a more thorough discussion of what fits into mid-level IRB review categories.

Convened Full Board Review

Convened IRB full board studies are when one of the following is true about the study:

1. The mobile software application or wearable alone or in combination with other items is being tested for safety or efficacy.

2. The mobile software application or wearable will be tested for new indications (i.e., off label use) or with a population (e.g., minors) that it is not cleared or approved by the FDA to be used with.

3. The mobile software application or wearable alone or in combination with other items needs an investigational device exemption (IDE) from the FDA or an abbreviated IDE from the NC State IRB convened full board.

4. The mobile software application or wearable alone or in combination with other items is a significant risk (SR) device as determined by the IRB or the FDA.

5. The research procedures themselves are more than minimal risk to participants.

6. The device is a significant risk (SR) device.

7. The research procedures are minimal risk to participants, the device is a nonsignificant risk device, but the proposed research does not fit into one of the established federal research categories that is eligible for expedited review.

Examples of convened IRB full board medical device studies:

- Individuals with and without spinal cord injuries test an exoskeleton that stimulates back and leg muscles to assist the wearer with walking. This is a convened full board study because the purpose-built wearable (i.e., exoskeleton) is being tested for efficacy and can cause burn injuries to participants during use, which is more than minimal risk research.

- Teens with poorly controlled asthma use an Apple Watch, a purpose-built mobile software application, and sleep-tracking mat to monitor and record respiratory function, heart rate, and sleep awakenings. The mobile software application helped users reflect on symptoms and triggers and provided tools to respond to flare-ups. This is a convened full board study because it targets a contextually vulnerable population, records potentially

sensitive information with mandatory reporting responsibilities, and is testing the device combination for efficacy.

More detailed information about studies that might go to the convened full board can be found in the NC State IRB unit standard on full board meetings (Word document), but to recap: if the mobile software application or wearable is being tested for safety or efficacy, the study or the device is more than minimal risk, or the device will be used off label, the study is a convened full board study.

What to Address in the IRB Application

We expect that you will address the following in your IRB application:

1. Scientific validity and merit – why this study, why now, and why this is the best next step in the phase of the research.

2. Participant selection – how you're selecting participants who are the best to answer your research question, not just those that are convenient, like students.

3. Consent process – so participants are empowered to make the best choice for them.

4. What the research risks and benefits are.

5. Data management plan – multimodal, real-time data that is the nature of mobile software applications and wearables functioning as medical devices have unique challenges for data privacy and security.

6. For research protocols that will need an abbreviated IDE for one or more mobile software applications or wearables in the study:
    - The IRB application must discuss for each medical device:
        - if the device is approved or not by the FDA;
        - If the device uses component parts that are FDA approved or not and if they are approved for the proposed combination that will be used in the study;
        - how the device is being used and whether the usage is "on label" or "off label";
        - if the device is or is not commercially available;
        - if the device will be modified or purpose built, by the research team or by others prior to use with human subjects;
        - if the device's safety or efficacy will be assessed and how it will be assessed;
        - if the device development or modification will benefit (financially or otherwise) any member of the research team or the project sponsor/funder;

- if the device is being used only as a tool for data collection in the research or if the device is being tested for safety and efficacy;
- what data the device is collecting/recording;
- if the data will remain on the device or if it will be communicating to or sharing the data it collects with other devices and/or people;
- how the device is donned and doffed, if applicable

- In the consent form
  - Precise description of the data used, collected, and shared by the medical device
  - Once the wearable/mobile software application is developed, how it will be supported, patched and upgraded to ensure participant safety and data integrity
  - How is the wearable is put on and taken off
  - Investigational device(s) information:
    - How the device is being used
    - If the device is approved by the FDA for how it will be used or not
    - If the device is being tested for safety or efficacy data
    - If the device was developed by the researcher or the researcher will benefit financially from the research results
    - If a device is purpose-built and not approved by the FDA, consent should state that the device is not approved by the FDA
    - Statement that the FDA has the right to inspect the research records

- Upload to the IRB application (NOTE: A longer list is provided in Appendix B, this is just the short list of device research specific materials the IRB must see)
  - Data and access security plan (DASP) from NC State's Security and Compliance (if needed)
  - Application software informed consent form addendum (Word document) as applicable
  - Completed medical devices used for research form (Word document) for each medical device
  - Completed participant procedures document (Word document)
  - Completed code review form (Word document) if the mobile software application or wearable that is a medical device is commercially available but modified (it does not matter who modifies it) OR is purpose-built. Please also review the IRB's applications and software guidance (Word document).
  - All device manuals
  - Homegrown, purpose-built, and modified application software information sheet (Word document) as applicable

        - Researcher personal device use attestation (Word document) as applicable

7. For research protocols that will need an IDE from the FDA for one or more mobile software applications or wearables in the study:
    - In the application, include the following information:
        - Device being tested for safety/efficacy
        - How the device is being used (on or off label)
        - If the device is commercially available
        - If the device is or is not approved by the FDA
        - If the device is developed by the researcher
        - If the device uses component parts that are FDA approved, modified, or purpose-built
        - IDE number proof from sponsor or FDA (proof must come from the FDA if the device is under an investigator held IDE)
        - Medical devices used in research form (Word document) for each device
        - For experimental devices:
            - State: "There is a label on the experimental device with the statement "Caution, Investigational device. Limited by Federal (or United States) law to investigational use." *Make sure the experimental device is labeled as such.*
            - State: "No member of the research team will promote or market the experimental device."
            - The informed consent includes the following information about the experimental device <insert information from your consent form>.

    - In the consent form
        - Statement that the FDA can inspect research records.
        - Details about the device that a reasonable person would want to know *in lay language:*
            - If the device is being tested for safety/efficacy
            - If the device is approved or not approved by FDA
            - If a device is modified or purpose-built and not approved by the FDA, consent should state that the device is not approved by the FDA
            - What the specific risks and benefits of the device usage are

    - Upload to the IRB application (NOTE: A longer list is provided in Appendix B, this is just the short list of device research specific materials the IRB must see)
        - Data and access security plant (DASP) if needed
        - Application software informed consent form addendum (Word document) as applicable

- Completed medical devices used for research form (Word document) for each medical device
- Completed participant procedures document (Word document)
- Completed code review form (Word document) if the mobile software application or wearable that is a medical device is either commercially available but modified (it does not matter who modifies it) OR is purpose-built. Please also review the IRB's applications and software guidance (Word document).
- All device manuals
- Homegrown, purpose-built, and modified application software information sheet (Word document) as applicable
- Researcher personal device use attestation (Word document) as applicable

Appendix A – NC State University Specific References

Listed below are the most referred to University-authored references for human subjects research proposing use of a wearable and/or mobile application. Depending on how your research is designed, they may or may not apply to your study. This appendix is not a comprehensive list of all University guidance, IRB unit standards, or IRB guidance. Researchers are responsible for knowing the standards and guidance that are applicable to their study.

Select University Guidance

- Human Subjects Research (opens in a new window)
- Principal Investigator Eligibility and Standing (opens in a new window)
- Privacy and Security of Protected Health Information (opens in a new window)
- Endpoint Protection Standard (opens in a new window)

Select IRB Unit Standards

- Adult Consent, Minor Assent, and Parental Permission (Word document)
- Clinical Trials (Word document)
- Cooperative Research, Reliance Agreements, and Single IRB (Word document)
- Expedited Review Procedures (Word document)
- Health Insurance Portability and Accountability Act (HIPAA) (Word document)
- IRB Review and Approach for Research Involving Human Subjects from the Joint Department of Biomedical Engineering (BME) (Word document)
- Medical Devices (Word document)
- Pilot Studies and Feasibility Work (Word document)
- Post-Approval Monitoring (Word document)
- Renewals, Amendments, Closures, and Transfers (Word document)
- Research Involving Minors (Word document)
- Unanticipated Problems and Adverse Events (Word document)

Select IRB Forms

- **Artificial Intelligence (AI)**
  - Participant Information Sheet (Word document)
  - Supplemental Information Form (Word document)

- **Applications and Software**
  - Code Review Form (Word document)
  - Application Software Informed Consent Addendum Template (Word document)
  - Homegrown, Purpose-built, and Modified Application Software Information Sheet (Word document)
  - Personal Device Use Attestation Form (Word document)

- **Cooperative Research**
  - Cooperative Multi-Site Study Checklist (Word document)
  - Cooperative Research Site Context Worksheet (Word document)

    - Institutional Authorization Agreement Form (Word document)

- **Health Insurance Portability and Accountability Act (HIPAA)**
    - HIPAA Authorization and Revocation Form (Word document)
    - Internal PI Requesting Access to NC State Held HIPAA Records Form (Word document)
    - Request to Waive HIPAA Authorization Form (Word document)

- **Medical Devices**
    - Medical Devices Used in Research Form (Word document)

- **Research with the Human Body** (e.g., BME protocols, Exercise Science, etc.)
    - Participant Procedures Template (Word document)

Select IRB Guidance Documents

- NIH Grants and the IRB (Word document)
- Biomedical Engineering (BME) Directions for IRB Review, Approval, and Reliance Agreements (Word document)
- Phased and Staged Research (Word document)
- Use of Applications and Software for Research with Human Subjects (Word document)
- Use of Artificial Intelligence (AI) and Generative AI (GAI) in Human Subjects Research (Word document)
- Secondary Data and the IRB (Word document)
- Images and Recording in Research with Human Subjects (Word document)

Appendix B – eIRB Application Directions

Directions for completing the eIRB application for a non-exempt study that involves the use a mobile software application or wearable that meets the definition of a medical device.

Title tab

"Project Title" question: List the research study title which (ideally) should match any project title funding proposal. In addition:

- Add the project title prefix "[Funded]:" if the study is funded from any source: federal, state, foundation, non-profit organization, etc.

- Add the project title prefix "[.118 Determination Request]:" if the study has received a notice of funding from the National Science Foundation (NSF) and a time sensitive request for IRB approval but the study is not fully developed or ready for IRB review. Follow further instructions for how to apply for a .118 determination on the IRB website (opens in a new window)

- Add the project title prefix "[Just-in-Time Request]:" if the study has received a notice of funding from the NIH and a time sensitive request for IRB approval but the study is not fully developed or ready for IRB review. Follow further instructions for how to apply for a Just-in-Time request on the IRB website (opens in a new window)

- Add the project title prefix "[DoD Affiliated Research]:" for all studies that are supported and/or funded by the Department of Defense.

- Add the project title suffix " – Phased Study" for all phased and staged research protocols

"Source of funding" question: List source of funding if you have it or state "None." If the research is funded, link to the sponsored project record on the Title tab. If the study is funded but does not have a sponsored project record number, detail the funding source and flow on the second narrative response box on the Description tab.

"NCSU Faculty point of contact" question: Select the point-of-contact from the drop-down list. If a faculty member is not listed in the menu, contact the IRB office (irb-coordinator-pre@ncsu.edu) for assistance.

"Add New Personnel Record" button: Enter the name, NCSU email, and Unity ID for NCSU members of the research team that the PI wishes to have editing access to the eIRB application and to receive automated emails from the eIRB system. This is typically where student researchers are listed if the research is for their master's thesis, dissertation, or capstone project.

“Does any investigator associated with this project have a significant financial interest in, or other conflict of interest involving, the sponsor of this project?” question: Answer No if the research is not sponsored.

“Add/View Supporting Documentation” button: Click this button to access the area of the application where all supporting documentation will be uploaded. Refer to the Supporting Documentation section of this appendix for further guidance on what one might need to upload. All supporting documentation, with the exception of human subjects research training certificates, individual investigator training materials, completed ancillary review materials (e.g., scientific merit, code review, context review, data & access security plan (DASP), etc.) should be uploaded as editable Word documents – clean files if never approved by the IRB and changes tracked if part of an formal protocol amendment to an already approved IRB study where the amendment proposed requires the formerly approved document to change.

“Renewal/Amendment Request Form” button: This button will populate only after the IRB protocol is initially approved by the IRB office. You will click the button if you wish to renew a convened full board study and (very rarely) studies reviewed at lower levels where nothing has changed or for any level of IRB reviewed study where you’d like to make changes to the approved protocol. The changes can be minor in nature such as adding research team members or more significant such as changes to the participant population or research procedures. Answer all questions for the request you are making: a protocol renewal, a protocol amendment, or both sections if you wish to renew and amend a protocol. Remember that for amendments, you have additional steps beyond filling out the amendment request form – you’ll need to add additional paragraphs in relevant sections of the eIRB application tabs (instructions are provided in the eIRB screenshot tutorial) and upload all new and revised supporting documents that reflect the proposed changes.

“Add New Sponsored Project Record” button: Click this button to view a pop-up window where you will enter the PINS, SPS, or 6-digit account number of the sponsored project record(s) associated with the project. Once the number is entered click the “Save” button. If there are multiple numbers to enter, click the “Add Another Sponsored Program Record button” and type each of additional numbers one at a time and click the “Save” button. Once you have entered all of the numbers and saved them, click the “Close” button. Double-check that all of the sponsored project records associated with the research are now listed on the Title tab of the application. If they are not, please email sps@ncsu.edu and include your IRB protocol number. This is not an issue that IRB office staff can resolve for you as the information populating to the IRB application comes from a different electronic system that the IRB office doesn’t have access to, much less control over.

Description tab

“In lay language, briefly describe the purpose of the proposed research and why it is important” question: This description should be no more than 5-6 sentences -

please NO citations and DO NOT copy and paste from your dissertation prospectus/grant proposal. Discuss the purpose of the study (1 sentence), what it is contributing to the scholarly discourse/literature that is currently missing (1 sentence) and, if appropriate, why it is the next appropriate step to research (1 sentence if not discussed in the sentence about contribution to scholarly discourse), and a few sentences providing a broad overview of the study. In addition:

> **For primary data collection protocols**, you will discuss who is targeted for participation and a brief, succinct overview what will they do as part of the research study.
>
> **For phased research studies, including pilot studies:** Use and complete the following fill-in-the-blank: “This is a phased research study and I/we am applying for the <insert information – e.g. pilot phase, phase 1, phase 2, etc.> <Provide the research question(s) and goal(s) of the pilot study including explanation of why a pilot study is necessary, what the clinical endpoint(s) will be, and a very brief (1-2 sentences) overview of research procedures>. Uploaded for review are all research procedures for this phase. No other research activities will occur for this study until an amendment detailing the unspecified research procedures and the corresponding supporting documentation is reviewed and approved by the NC State University IRB office.”
>
> **For secondary data protocols:** State that this is an application for secondary data, what the secondary data set(s) contain in terms of content and identifiers (direct and indirect), how many participants are in the data set, and what you’re going to do with the data set(s) you’re requesting to use for research purposes.
>
> **For protocols that will be using a medical device:** Describe the project, state that it isn't a clinical trial or studying safety/efficacy of any device if true (not exemption if you are), & include the statement, "Please see uploaded procedures documents for eIRB content. Most of the application is blank except for the boxes that need to be answered. All documents are uploaded for review."
>
> **For amendment requests for protocols that were already approved by the IRB office:** Do not delete the verbiage that is already present but add an additional paragraph beginning with the phrase “Amendment request (Month and year request opened on the Title tab, e.g., September 2025):” and then briefly describe what is changing within the context of the question.
>
> > *Note*: Amendment paragraph must appear in every narrative response in each application tab where you're applying to change your approved IRB protocol. You should not use the amendment paragraph if you are revising a protocol that was never approved by the IRB.

“Does any member of the project team who is responsible for the design, recruitment, consent, implementation of intervention, interaction with

participants, or those handling identifiable private information under this IRB protocol" question: In addition to addressing any significant financial conflicts of interest requested above, name what funding source(s) you have and describe funding flow here ONLY IF you can't link to a sponsored project record on the title tab and your protocol is funded. Yes, internal funding from NC State University counts as funding.

"This research qualifies for exemption" question: This is a no because research with a medical device is not eligible for exemption.

"Is this research being conducted by a student" question: If yes, please answer the additional questions that pop up including if the research is for a course or thesis/dissertation/capstone and what plans there are to use the data beyond the class assignment if the research is for a class.

"If you anticipate additional NCSU-affiliated investigators" question: Name anyone here that is not listed on the title tab as the faculty advisor or additional personnel if they are at NCSU and *engaged* in the research protocol--e.g., involved in recruitment, consent, interacting with participants, collecting data, or handling any re-identifiable/identifiable research data. Anyone listed on the IRB application who is at NC State University must have their human subjects research training uploaded to the protocol and it must be complete for the IRB office to review the study.

Here's the link to the IRB guidance document for current human subjects research training requirements:
https://drive.google.com/file/d/15On0UevTEaZz9cXk9pVPdSstZPFgjnbO/view (Word document)

"Will the investigators be collaborating with researchers at any institutions or organizations outside of NC State?" question: For cooperative research, answer the additional questions in addition to reviewing the NC State University IRB website page on cooperative research.

> **"List collaborating institutions"** question: Name the persons, institution/NGO they're at, and what they will be doing on your protocol and what you're doing on the protocol. This will help the IRB determine whether we should be in the IRB of Record for the protocol or the relying IRB. For more information about IRB of Record and relying IRB, see the "Cooperative Research" section of the NC State University IRB website:
> https://research.ncsu.edu/administration/compliance/research-compliance/irb/cooperative-research/ (opens in a new window)
>
> **"What is NCSU's role in this research?"** question: If your cooperative research will involve more than one site and NCSU will be the reviewing IRB, a site context worksheet must be completed and uploaded to the supporting documentation. The worksheet can be found on the "Cooperative Research" section of the NC State University IRB website:

https://research.ncsu.edu/administration/compliance/research-compliance/irb/cooperative-research/

Make sure to upload a completed reliance and individual investigator agreement form to your supporting documents for all individuals engaged in the research, along with CITI training for all NCSU research team members. You do not need to upload the training for individuals who are under the purview of another IRB with an FWA number. If an individual investigator agreement is necessary for your protocol, you will also need to upload the individual investigator's CITI training (preferred and, in federally funded cases, required - alternative training cannot be accepted) or your adapted PPT training presentation and the investigator's training attestation form for review. Read more about the individual investigator process on the "Cooperative Research" section of the NC State University IRB website: https://research.ncsu.edu/administration/compliance/research-compliance/irb/cooperative-research/

"Describe funding flow" question: If no funding, state "None," but if there is funding, describe it and it should match what you say on the title tab (you must link the sponsored project record to the protocol or discuss the funding on the Description tab) and the funding must be disclosed in your consent form. Note that funded research often has additional human subjects research training requirements that you, not the IRB office, are responsible for identifying and ensuring compliance with. Please note that funding flow can change who the IRB of Record is even if the awarded institution is not the primary lead on the funded project.

"Is this international research" question: If yes, answer the additional questions.

- You'll want to review the countries on the sanctions list and indicate if the country you want to do research in is on the list: https://home.treasury.gov/policy-issues/financial-sanctions/sanctions-programs-and-country-information (opens in a new window).
- This isn't under the IRB's jurisdiction, but if you will be importing equipment to any country – even if it's your own personal equipment such as a laptop - you must fill out this form: https://research.ncsu.edu/administration/compliance/research-compliance/export-controls/export-control-determination-request/ (opens in a new window)
- The context reviewer you list doesn't need to have a Ph.D. but they must have the expertise to appropriately evaluate the risks to participants posed by the protocol. The context reviewer cannot be a person who is a member of your research team or the host organization or research site or who stands to benefit financially from the research or otherwise has a conflict of interest. Once IRB staff have communicated to you that the IRB application is ready for final review, you will facilitate the context review by contacting the listed reviewer, asking them to review your research proposal and all supporting documents when the IRB office marked "for review." The reviewer completes a written evaluation using the

NC State University IRB form and provide the form to you in a locked (uneditable) format, such as a PDF. You will upload the review to the supporting documentation section of your application for IRB review. See the "Step 3: Application Review Process" page (opens in a new window) for the forms and instructions for local context and participant context reviews. Note: The reviewer is not compensated for their labor by the IRB office or NC State University.

Populations tab

"General populations" question section: Click "Yes" if the population is able to participate in the study even if they are incidentally included. In addition:

"NCSU students, faculty, or staff" question: You must click yes if you are recruiting through NCSU means even if the inclusion criteria do not specify that one must be a student (e.g., campus fliers, research announcement to student group(s), recruitment of students in a class/cohort/major/college, use of SONA pool, etc.)

"Are you asking participants to disclose information about other individuals" question: You must click yes if you will be getting information about people other than those who directly consent to be in the study or whose consent was waived by the IRB, for example qualitative data that mention people other than the participant

"Minors" question: You must click yes if minors are involved in your research and you need to list the age range of the minors involved and discuss if any of the minors could be wards of the state.

"Does this study involve people who are also incarcerated, involuntarily detained or committed, or are in a program or hospital as an alternative form of sentencing?" question: You must answer "Yes" if the incarcerated persons are included in your study.

"Vulnerable populations" question section: Only click yes if the population is specifically targeted for inclusion in your research study, not just incidentally included. All studies must answer the "Pregnant women" and "Fetuses" questions regardless of the type of non-exempt study that will be conducted or the type of medical device(s) used in the study. In addition, there are some vulnerable populations that if you click yes, you may need to answer additional questions. They are:

"Students" question: Students mean students at NCSU or elsewhere. If targeting your own students, you must articulate why you must target your own students to answer the research question (convenience is not a valid justification) or if only advertising on the NCSU campus, why students are critical to answering the research question and why the general population will not suffice. You will need to answer the additional questions that pop up about where the

research occurs, how the research occurs, if instructional time or course credit is involved, gatekeeper permission for the research study, student records access for research, and records release permission.

“Employees” question: Employees means those you are targeting because of their job or professional expertise. Answer the additional questions that pop up if you answer “Yes” under the population “Employees” including details of how employees will be recruited, the involvement of the employer in research procedures and their access to the research data, and how employee identities will be protected from the employer’s reidentification to the greatest extent possible.

“Impaired decision-making capacity/Legally incompetent” question: Click yes if this population is targeted and answer the additional question about how competency will be assessed and informed consent sought. Researchers are generally not equipped to assess legal thresholds of cognitive competence unless they are a Board-certified neurologist.

“Mental/emotional/developmental/psychiatric challenges” question: People with mental/emotional/developmental/psychiatric challenges can include irreversible (developmental anomalies) and reversible (anxiety, depression) health conditions. Answer the additional questions about the unique challenges and risks for the participant population and how you will facilitate equity in the research for the population that pop up when you answer “Yes” to this population.

“People with physical challenges” question: People with physical challenges can include irreversible (amputation) and reversible (obesity) conditions. Answer the additional questions that pop up when you answer “Yes” under the population “People with physical challenges” about the unique challenges and risks for the participant population and how you will facilitate equity in the research for the population.

“Non-English speakers” question: If you are targeting individuals whose native language is not English, you’ll need to describe the procedures you’ll implement to overcome language barriers. This can include participant materials in native language (see verification of translation guidance on the IRB website) - don't translate documents until the IRB office says that your application is ready for final review to save time/labor), members of the research team who are native speakers or certified fluent speakers, use of translators, etc. If you’ll be using an interpreter, you’ll need to provide about the translator (who they are, relation to the community, why you have selected them for use, confidentiality measures being utilized). We need you to include all of this information so the IRB can assess conflicts of interest and whether it will affect participant voluntariness through preexisting social or cultural bonds.

“Explain the necessity for the use of the vulnerable populations listed” question: For every “Yes” selected for the vulnerable populations identified in your IRB application, justify why you need to target them to be able to answer your research question(s). Convenience isn't an acceptable justification.

Consent tab

“State how, where, when, and by whom consent will be obtained” question: Discuss how consent will be sought and documented for each adult participant group in the response box. Make sure that the appropriate non-exempt consent forms using the linked template are uploaded as supporting documentation for the IRB to review.

“If any participants are minors” question: Discuss how parent/guardian permission and minor assent will be sought and documented in the response boxes. Make sure that the appropriate forms (parent/guardian permission and all applicable minor assents using the linked templates) are uploaded as supporting documentation for the IRB to review.

“Are you applying for a waiver of the requirement for consent” question: If you will not be seeking consent or parental permission for research, click “Yes” to a waiver of consent and provide a justification for why the research is minimal risk to participants, why waiving their right to consent will not negatively affect participants’ rights or welfare, why the research is not practicable without a waiver of consent, and why the research is only practicable with the use of identifiable/re-identifiable data.

“Are you applying for a waiver of signed consent” question: If you will be getting consent, parent/guardian permission, and/or minor assent for research in a format other than a written signature, click “Yes” to a waiver of signed consent and answer the additional question that pops up. Common additional links beyond a signed consent form include identifiable FERPA records, audio/video recordings, master list/crosswalk, etc.

“Are you applying for an alteration” question: Alterations of consent is when informed consent occurs later in the research process than is typical, such as at the end of a data collection procedure because a study has deception in it. If there will be an alteration of consent in your study, you must click “Yes” and tell the IRB how the consent process will be altered, who the alteration of consent affects (all participants? some (e.g., one group of) participants?), why the research cannot be done without an alteration of consent, why the research is minimal risk to participants, why the alteration of consent will not negatively affect participants’ rights or welfare, and why the research is not practicable without the alteration of consent.

“Is there any deception of the human subjects” question: Deception is when information about the study is either omitted or presented in an intentionally false manner to participants. If the study will have deception, tell the IRB what the deception will be, why deception is necessary to answer the research question, how research

participants will be debriefed about the deception and reconsented for the use of their data, and if participants will be given the option to have their data destroyed if they do not want to be in the study after the debriefing. If they will not have a choice to have their data destroyed, you must provide a justification for why this is not an option. Remember to upload the debriefing script to the IRB application's supporting documentation section.

Procedures tab

State here "Please see uploaded participant procedures document" (Word document) for all response boxes on this tab except two:

1. If you answer "Yes" to any relationship between the researcher and participants (e.g., teacher/student; employer/employee; colleagues, etc.) you must answer the two additional questions that pop up.
    a. You'll need justify targeting people you know for research and how you're going to mitigate the risks for coercion into research and preserve participant voluntariness.
    b. You'll need to explain how data quality will be preserved despite the pre-existing relationship that you have with the individuals you're targeting for research.

2. If you'll be using secondary data (already in existence or will exist in the future, e.g., class assignments), answer the question about secondary data. A fill-in-the-blank that you can use is:

    The secondary data set that I/we wish to access is <insert name of data set, e.g., "pre-lab assignment," "lab notebook," "midterm grade," etc.> and it was/will be collected <insert information describing how it was/is collected and when>. I/We have gatekeeper permission from <insert gatekeeper's name> to access the data for research purposes. I/We will access this secondary data <describe how you will access it>. I/We will transfer the data to <tell the IRB where you are transferring it to, NC State Google Drive, external/internal encrypted drive, etc.> by <describe processes for transferring the data--e.g., VPN, encryption, etc. NOT EMAIL>. I/We will store this data <tell us where you're storing it>. I/We will destroy my copy of this secondary data when <tell us when> by <tell us how>. This data <select one: is or is not> subject to FERPA and <select one: is or is not> to HIPAA. I/We <select one: do or do not> need a data use agreement (DUA) or material transfer agreement (MTA) because <provide reason>. <Discuss identifiability of the data set – is it inherently identifiable because direct identifiers are on the data, indirectly identifiable due to research team member's access/role/expertise, indirectly identifiable due to technological tools or triangulation of indirect data points, or not identifiable – and justify why>.

Data Security tab

Answer all radial and narrative response questions on the Data Security tab UNLESS a completed data & access security plan (DASP) form to your supporting documentation because you're collecting red or purple-level data. If you submit a completed DASP, you do not need to complete this tab of your IRB application.

If you do need to complete this tab, for the narrative responses:

"Describe all participant identifiers" question:

1. List all direct and indirect identifiers of participants and third parties that you are collecting throughout the research process: recruitment, screener, consent, each mode of data collection (survey, interview, eye tracking, website usage data, etc.), and any secondary data. Direct identifiers are things such as name, email, phone number, IP address, Unity ID/student ID/social security number, voice recording, video recording, etc. Indirect identifiers are things such as race, sex, gender, sexual orientation, birth year, income, some general geographic locations (such as city or state), major/degree program, year in school, unique stories that could be triangulated together to re-identify individuals (participants or third parties), a user's activity on a particular website or in an online group, etc. A data source can contain direct and indirect identifiers.

2. Tell us why you need each direct and indirect identifier to answer your research question.

3. Tell us when you will get rid of each identifier from your data set, when in the research process, and how you will do so. We expect that you will get rid of all direct identifiers. If you plan to retain indirect identifiers, state that and how you will protect participants from being re-identified.

Note: If you are struggling with knowing what an identifier is, please review the IRB guidance on identifiers: https://docs.google.com/document/d/1DhQ2xDQs8daep9SKmKqiTFM6bLZFu3Tu/edit#heading=h.gjdgxs (Word document)

"If recording identifiable information" question: Links between identity and the data include one's master list/crosswalk, research recordings (audio/video/screen/physiological), photography of participants, EEG recordings with the participant's name on them, and surveys/e-data that collect direct identifiers on them (name, email, MTurk/SONA/UNITY ID, IP addresses associated with them, etc.). Please tell us all of the links that you will have, why you need those links, and when you will get rid of each of those links in the research process.

"Discuss if you'll be working with your departmental IT" question: Data management is one of the federal criteria for human subjects research--you

cannot say N/A or leave this question blank. If you struggle with answering this question, seek support from OIT's Help Desk and include your IRB protocol number.

For any study that collects highly- or ultra-sensitive (red or purple) data OR needs/has a DUA (data use agreement), MTA (material transfer agreement), CoC (certificate of confidentiality), NIH DMSP (data management and sharing plan), please upload the completed data and access security plan (DASP) form to your supporting documentation that OIT staff via the Service Now portal developed for you. State in response to this question prompt the following "Yes, I have uploaded a data and access security plan is uploaded to the protocol's supporting documents that was developed by OIT staff member <insert OIT Security and Compliance professional name>."

For studies where a separate data & access security plan form is not required to be uploaded to your supporting documents, discuss the following in your answer:

1. What types of devices (NCSU managed, personal, or both) that will access the data. You must consider all members of the research team, including the faculty advisor for a student protocol.

2. If personal devices will be used, detail established data protection process that will be employed, such as regularly updated software, hardware, malware protection, etc.

3. Provide details for the types of research data that will be collected or accessed for research purposes:

    For digital information, say that you will:
    - Use password protection for all files containing research data
    - Use password protection for all devices housing research data
    - Use 2 Factor Authentication for accessing research data
    - Use VPN when using the internet to transfer, access, upload, or download to research data files and folders
    - Use NC State versions of Google Drive, Zoom Pro, Qualtrics or RedCap accounts where appropriate
    - Use of encryption for data files with direct identifiers, containing master list/crosswalks/codes linked to participant IDs, or files with highly sensitive (“red”) or ultra-sensitive (“purple”) data

    For hard copy data:
    - Discuss if the hard copy research data has direct identifiers on it or if those are removed and how
    - Discuss where the hard copy research data is stored and how it is protected (locked in drawer? locked in an office? badge scan to get in building?)

- Discuss the master list/crosswalk if it is a hard copy - discuss where it is stored and how it is kept separate from the data files
- Discuss how the hardcopy data and hardcopy master list/crosswalk are transferred if transferred (from the moment it is collected or generated to when it is destroyed) – please do not transfer them together
- Discuss who can access the hard copy research data and why
- Discuss how and when you will securely destroy your hard copy research data

3. Discuss when and how the research data is transferred.

    a. For digital data, how it travels from one platform to another and between devices (you will likely transfer data several times throughout the course of the research project). For example, recording an interview either within the NC State managed Zoom application or to a local drive (not cloud storage) and then transferred to the NC State managed Google drive for data cleaning and analysis.

    b. For hard copy data, how the data is transferred from the data collection point to the researcher's possession and then into a location to facilitate data cleaning and analysis.

4. Discuss who will have access to research data and why. You must articulate the access all members of the research team will have, including the faculty advisor, and any third parties (e.g., mobile software application and wearable developers, consultants, transcriptionists, etc.)

5. Discuss when the research data will have direct IDs stripped if your data will always be re-identifiable (e.g., qualitative interviews, surveys with detailed demographics, etc.)

6. Discuss when the research data will be securely destroyed and how it will be destroyed

7. Discuss if you will consult with NC State's OIT department via the help@ncsu.edu service if/when data management issues arise in the protocol

"Describe any ways that participants themselves or third parties discussed by participants could be identified indirectly from the data collected, and describe measures taken to protect identities" question: Use the following fill-in-the-blanks to answer the question.

Participants can be reidentified through the following data points list each of the data points that could re-identify participants on their own, such as a participant's

name, or re-identify a participant in conjunction with other research data that is collected and any research methods that could be contributing to re-identification potential, such as, small participant pool, triangulation of data, uniqueness of participants' stories, use of secondary data including student records data subject to FERPA, research methods such as focus groups, etc..>. The probability of reidentification occurring is <select one: highly probable, somewhat probable, unlikely, highly unlikely> because <insert reason>. The severity of impact if reidentification occur would be <select one: life-threatening/disabling, severe and undesirable, moderate, mild> because <insert reason>. If reidentification occurs, the harm would be <select one: reversible or irreversible> because <insert reason>. The duration of harm would be <provide information> because <insert reason>. The risk(s) of reidentification will be mitigated by <insert mitigation strategies that will be employed>.

Third parties can be reidentified through <provide reason>. The probability of reidentification occurring is <select one: highly probable, somewhat probable, unlikely, highly unlikely> because <insert reason>. The severity of impact if reidentification occur would be <select one: life-threatening/disabling, severe and undesirable, moderate, mild> because <insert reason>. If reidentification occurs, the harm would be <select one: reversible or irreversible> because <insert reason>. The duration of harm would be <provide information> because <insert reason>. The risk(s) of reidentification will be mitigated by <insert mitigation strategies that will be employed>.

“For all recordings of any type” question: Make sure that you answer all of the above sub-questions for each recording method (audio, video, photography, EEG/MRI, screen recording, motion sensing, etc.) you plan to use for the protocol. If you are not planning on any recording, state here, "This study is designed without recording of any sort."

Note: Video is riskier than audio recording, so federal law requires a justification for utilizing video recording explaining why the audio recording alone will not suffice to provide you the data you need to answer your research question. You will provide that justification in your response here after you answer all of the bullet questions above for video recording. This is a federal requirement. Please review the recording and images in research IRB guidance (Word document).

“Describe how the data will be reported” question: Tell us how the data will be reported out to others beyond the research team. Some examples are reporting data in aggregate, themes, quotes, etc. If reporting data in aggregate, what is the smallest N you will report in any category? For qualitative research data, how will you protect participants from being re-identified?

“Will anyone besides the PI or the research team have access to the data (including completed surveys) from the moment they are collected until they are destroyed?” question: Who has access to what research data, when

do they have access to the research data, why do they have access to the research data, and what will they do with the research data? For example, the PI (and faculty advisor where student is the PI) likely will have different access to the data than other research team members, and that access will be greater than the broader scientific community or funder (in most cases). Be sure to parse data sharing out here and make sure it matches what you say in the consent form. Consider also what data you'll need to share for compensation, transcription, member checking, and data sharing (particularly if broad consent was sought and given or if the terms of your grant require data sharing).

Risks and Benefits tab

Answer all of the radial button questions listed identifying the risks in your study due to either research design or how the data is reported and shared with others. If you are struggling to answer these questions, consult with your faculty advisor (if applicable) and review the IRB Basics Part II slide deck available through REPORTER after registering for the asynchronous training.

“Describe the nature and degree of risk that this study poses” question: If no “Yes”es were selected above in the radial button answers, you can say here, "There is minimal risk associated with this research." If there are any “Yes”es selected above in the radial button responses, here you need to identify what the risk is, what the likelihood of harm and severity could be if the risk happened, if the harm would be reversible or not, and how you will mitigate the risk as much as possible for each "Yes" you indicated above. Address whether the risk is a result of the research design or in the use of the research data and what type of impact the risk will make on the participant during the research activities or afterwards. Make sure the risks listed here match your consent form's risks and benefits section.

“If you are accessing private records” question: Answer this question by detailing what private records you wish to access for research, how you accessing them, what information you need from the records, how will you record and store the research data in such a way that identities are protected, and detail what laws these private records subject to. The content may or may not overlap with one’s response to the secondary data question on the Procedures tab of the eIRB application.

“If any of the study procedures could be considered risky in and of themselves” question: For example, anemia is a potential adverse effect of phlebotomy during participation in research where blood draws occur, so you would discuss how you are trying to prevent that from occurring with your participants through study design. So too with other study procedures that are inherently risky.

“Describe the anticipated direct benefits” question - Direct benefits are benefits participants get because of the research intervention(s) - not just participating in the research alone. Most research does not have a direct benefit to participants--this does not mean that the research has no value. Compensation is not a benefit of research.

“If no direct benefit is expected for participants describe any indirect benefits that may be expected” question: Discovery, education for the researcher/other scholars, and innovation can all be indirect benefits. Remember, a study must have more benefit than it has risk for the IRB to approve the study.

Compensation tab

“Describe any compensation that participants will be eligible to receive” question: If there is no compensation offered, state that here. If you choose to compensate participants (monetary or otherwise, e.g., course credit, t-shirts/stickers, pre-packaged food, et al), please review the IRB guidance on incentives and compensation in research.

Offering compensation means that your data is not anonymous and (in many cases, though not all) that you will need to share identifiable data about the participant with people who are not on the research team (e.g., Visa, your accounting office at NCSU, sponsor/funder, the Internal Revenue Service (IRS), etc.) to compensate your participants. Make sure your compensation strategy stated here aligns with what your accounting office/sponsor policies are and what your IRB application and consent form says about data sharing.

Note: Collecting banking data or social security numbers is classified by NCSU OIT as ultra-sensitive purple data that an uploaded data & access security plan form MUST account for. Ideally, you would not collect this information at all.

“Explain compensation provisions if the participant withdraws prior to completion of the study” question: If there is no pro-rated compensation offered, state that here. If you choose to pro-rate compensation, discuss how it will occur. Make sure that your recruitment and consent materials match what you say here about pro-rated compensation amounts and mechanisms of calculation and delivery.

Supporting Documentation

In addition to completing all eIRB application tabs, make sure to upload the following files to the supporting documentation section of your eIRB application:

1. Valid, unexpired human subjects research training for all members of the research team, including the faculty point-of-contact for student research protocols, who are involved in the processes of recruitment, consent, data collection, or handling identifiable/re-identifiable participant data.

2. All recruitment materials.

3. All consent, parent/guardian permission, minor assent materials and forms.

4. Broad consent addendum, if applicable.

5. All participant communications materials (e.g., scheduling and reminder messaging, research compensation drawing winner and loser emails, post-visit aftercare instructions, participant debriefing materials if deception or incomplete disclosure will be in the study, etc.).

6. Participant procedures document for each participant group (Word document)

7. All research measures (e.g., data collection protocol(s), observation protocol(s), survey questions, interview questions, participant interventions and interactions, etc.) used in the study.

8. Member-checking materials, if applicable.

9. All compensation documentation materials (e.g., NCSU accounting form that either participants or members of the research team will complete to facilitate research compensation for participants et al).

10. Completed translation verification form (Word document) and translated documents, if applicable.

11. All manuals for the mobile software application(s) and wearables that meet the definition of a medical devices and will be used in the study with participants or identifiable participant data.

12. All terms of service and user agreements for mobile software applications used in the study.

13. A completed medical device used in research form (Word document) for each medical device that will be used in the study with participants and/or their identifiable data.

14. Information sheet(s)for participants with instructions on how to access, download, and safely use the mobile software application or wearable in the study – for further instructions, please consult the IRB guidance on applications and software (Word document), IRB guidance on artificial intelligence (Word document), and the IRB unit standard on medical devices (Word document) if the topic is applicable to the study.

15. Researcher personal device use attestation (Word document) if applicable.

16. Application software informed consent addendum (Word document) if applicable.

17. Completed code review form (Word document) for each modified or purpose-built mobile software application or wearable(s) that include digital component(s).

18. HIPAA participant authorization and revocation form (Word document) or request to waive participant authorization form (Word document), if applicable to the study.

19. Completed site context form (Word document) for all cooperative research projects including those with UNC-Chapel Hill and/or Rex Hospital that will be conducted on multiple sites, are appropriate for single IRB review, and where the NC State IRB will be the IRB of Record.

20. Completed IRB authorization agreement form (Word document) for all cooperative research projects including those with UNC-Chapel Hill and/or Rex Hospital that are appropriate for single IRB review and need either an executed reliance agreement or individual investigator agreement for one or more members of the research team.

21. Completed individual investigator training completion and attestation form (Word document) and the edited training materials (PowerPoint file) used if a member of the research team needs an individual investigator agreement, does not have access to CITI training, and the study is not funded now or in the future from any source.

22. Completed scientific merit review form (Word document) done by a subject matter expert that is unaffiliated with the research team or the project sponsor/funder if the study is affiliated or funded by the U.S. Department of Defense.

23. Documentation from the NCSU institutional animal care and use committee (IACUC) providing approval or oversight exemption for the use of vertebrate non-human animals are involved in the study.

24. Completed local context review form (Google document) or participant context review form (Word document), if applicable to the study.

25. Upload any of the following data management materials associated with the study if they are applicable:
    - Data and access security plan (DASP) drafted by NCSU OIT
    - Completed request to access NC State held HIPAA records form
    - Emergency Health and Safety (EHS) committee approval
    - Institutional Biosafety Committee (IBC) approval
    - Executed material transfer agreement (MTA)
    - Executed data use agreement (DUA)
    - NIH data management and sharing plan (NIH DMSP)
    - NIH Certificate of Confidentiality (CoC)