Title: Medical Devices
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Standard Operating Practice: 20

20.1 Executive Summary

Research with human subjects that investigates or evaluates medical devices must comply with the Food and Drug Administration (FDA) regulations and the regulations governing research with human subjects. All regulated research studies with human subjects must be conducted under an approved IRB protocol. This document provides information about NC State University's IRB's standard operating practice regarding medical devices.

20.2. Standard Operating Practice

All NC State University researchers completing research that tests the safety or efficacy of a medical device, where the procedures involve humans, must comply with the FDA requirements detailed in the Federal Register's sections 21 CFR Part 812 on investigational device exemptions (opens in a new window) 21 CFR Part 50 on protection of human subjects (opens in a new window), 21 CFR Part 56 on institutional review boards (opens in a new window), 45 CFR 46 on protection of human subjects in research (opens in a new window), and adhere to the standard procedures noted below.

20.3. Operational Procedures

20.3.a. Definitions

1. **Medical Device**: A medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:
    a. recognized in the official United States Pharmacopeia - National Formulary (USP-NF), or any supplement to the USP-NF;
    b. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals; or
    c. 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 which is not dependent upon being metabolized for the achievement of its primary intended purposes.

2. **Significant Risk Device (SR):** A significant risk device is an investigational device that: Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and

presents a potential for serious risk to the health, safety, or welfare of a subject; or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

3. **Non-Significant Risk Device (NSR):** A nonsignificant risk (NSR) device is not a banned device, and it does not pose significant risk to human subjects in research.

20.3.b. When FDA Regulations Do Not Apply to a Study

20.3.b.i. Study Examples

1. A researcher uses an FDA approved device to test a physiologic principle where no data is collected about the medical device.
2. A researcher uses an FDA approved device to address a research question and no data is collected about the medical device.
3. A researcher uses an FDA approved medical device for clinical purposes (e.g., monitor a side effect, measure treatment progress but there is no intent to collect safety or effectiveness data, and there is no intent or action to develop the device for marketing).
4. A researcher uses a medical device that they have developed and no safety or efficacy information about the device is collected by the researcher.

20.3.b.ii. Clarifying Device Classification and Use

1. In the IRB Application

a. The medical device is approved by the FDA, used within the FDA's scope of intended use, and no data is being collected about the medical device; OR
b. The medical device is approved by the FDA, used outside of the FDA's scope of intended use, and no data is being collected about the medical device; OR
c. The medical device is approved by the FDA, used within the FDA's scope of intended use, and the data is being collected from the device for clinical monitoring purposes and not for research data on safety or efficacy of the device or for device development or marketing; OR
d. The medical device has been developed by the researcher/research team, is not approved by the FDA, no safety or efficacy data about the device is being collected, and there is no intention to develop the device for marketing.

2. In the Consent Process and Form

a. The consent process and, if applicable, form must discuss if the medical device is approved by the FDA or not and how the device will be used in the study.

b. The consent process and, if applicable, form must explain if the medical device is being used as the device (where safety or efficacy data is being collected) or a tool (where safety or efficacy data is not being collected).
c. The consent process and, if applicable, form must disclose when a medical device has been developed by the researcher.

20.3.c. When the FDA Regulations Do Apply to a Study

FDA regulations apply to a study that is evaluating the safety or effectiveness of a medical device in human participants or human biospecimens. When a study is subject to the FDA regulations, there are requirements specific to the type of study conducted and the device studied.

20.3.c.i. Investigational Device Exemption (IDE)

1. An IDE is a regulatory submission to the FDA that, once approved, permits the investigational device to be used in a clinical study where safety or effectiveness data is collected.
2. An approved IDE also permits the investigational device to be lawfully shipped for the purpose of conducting clinical investigations.
3. IDE studies test the safety or efficacy of one or more medical device(s) and the device(s) are deemed to be “significant risk” (SR).
4. The research team must have approval from the IRB and the FDA before beginning their study that requires an IDE.

20.3.c.ii. Abbreviated Investigational Device Exemption (abbreviated IDE)

1. An abbreviated IDE is a study where an investigational device is (or devices are) being tested for safety or efficacy and the device(s) are determined by the convened IRB full board to be “nonsignificant risk” (NSR).
2. The sponsor or principal investigator makes the initial assessment of whether a device is SR or NSR. If there is no sponsor, the principal investigator should provide their own initial risk determination with justification to the IRB.
3. The convened IRB full board will determine whether the sponsor/principal investigator’s device designation is appropriate.
    a. If the convened IRB full board determines the device is SR, then the sponsor/principal investigator will be required to submit an IDE application to the FDA.
    b. If the convened IRB full board determines that the device is NSR, the sponsor/principal investigator does not need to file an IDE application with the FDA and only needs

approval from the IRB with a NSR device determination before beginning their study.

4. The FDA has the ultimate authority to determine if a device study presents “significant risk" or “nonsignificant risk.”
    a. If the FDA disagrees with an IRB’s determination that a device is NSR, an Investigational Device Exemption (IDE) application must be submitted to the FDA and fully processed before the device is used in a clinical study.
    b. If a sponsor/investigator presumes a device to be SR and submits an IDE application to the FDA, the FDA might disagree and classify the device as NSR. In these cases, the FDA will return the IDE application to the sponsor/investigator with the recommendation that the device should be presented to the convened IRB full board as an NSR device.
5. NSR device studies must follow the abbreviated IDE requirements (opens in a new window) in the Code of Federal Regulations 21 CFR 812.2(b.) that the device:
    a. is not a significant risk (SR) device;
    b. is not a banned device;
    c. is labeled in accordance with Code of Federal Regulations 21 CFR 812.5 (opens in a new window);
    d. is approved by the reviewing convened IRB full board with an NSR determination documenting why the device is a NSR device;
    e. usage is within the scope of IRB approval;
    f. is used only with participants who have given documented informed consent or for which the IRB has waived informed consent under the Code of Federal Regulations 21 CFR 56.109 (opens in a new window);
    g. is used in compliance with the Code of Federal Regulations 21 CFR 812.46 (opens in a new window) with respect to monitoring investigations;
    h. is used in compliance with the Code of Federal Regulations 21 CFR 812.140(b)(4)(5) (opens in a new window) for research records maintenance;
    i. is used in compliance with the Code of Federal Regulations 21 CFR 812.150(b)(1) through (3) and (5) through (10) (opens in a new window) for required research reports;
    j. is used in compliance with the Code of Federal Regulations 21 CFR 812.140(a)(3)(i) (opens in a new window) for documenting subjects’ informed consent;
    k. is used in compliance with the Code of Federal Regulations 21 CFR 812.150(a)(1), (2), (5), and (7) (opens in a new window) for reporting unanticipated

adverse device effects, withdrawal of IRB approval, informed consent, and accurate, complete, and current information to the reviewing IRB or FDA when requested; and

l. is used in compliance with the Code of Federal Regulations 21 CFR 812.7 (opens in a new window) prohibiting promotion and other practices.

20.3.c.iii. Exempt from Investigational Device Exemption (IDE) Requirements

1. Studies that are exempt from the FDA's IDE requirements do not require a submission to the FDA for an IDE nor do they require an abbreviated IDE
2. These are studies where a device is:
    a. not a transitional device and is in commercial distribution before May 28, 1976 that was used or investigated in accordance with FDA labeling and indications;
    b. a diagnostic device that is noninvasive, doesn't require an invasive sampling procedure that presents significant risk, doesn't introduce energy into the subject, and the device is not used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure;
    c. tested for consumer preference, modification, or combination with two or more devices in commercial distribution as long as the testing isn't putting subjects at risk or determining a device's safety or efficacy;
    d. solely for veterinary use;
    e. shipped solely for research on or with laboratory animals and labeled in accordance with the Code of Federal Regulations 21 CFR 812.5(c) (opens in a new window); or
    f. a custom device as defined in the Code of Federal Regulations 21 CFR 812.3(b) (opens in a new window) unless the device is being used to determine safety or effectiveness for commercial distribution.

20.3.d. IRB Requirements for All Studies Involving Medical Devices

All studies with medical devices must provide the initial risk determination made by the sponsor/investigator to the NC State University convened IRB full board. The convened IRB full board is responsible for reviewing the sponsor's/principal investigator's SR or NSR device determination for every investigational medical device in a study and for every study that involves at least one medical device unless the FDA has already made a risk determination for the study.

If the convened IRB full board disagrees with the sponsor's/principal investigator's determination, the convened IRB full board may modify the

determination. If the FDA made the SR or NSR determination, the FDA's determination is final.

Please see Appendix A of this document for further details about the medical devices used in research form that contains the risk determination details and process. Beyond the initial risk determination for all medical device studies, the information required to be included in the IRB application and supplemental documentation varies depending on the type of FDA classification the medical device has.

20.3.d.i. Studies that require an IDE from the FDA

1. The NC State University IRB application must state:
    a. that the study is measuring the safety or effectiveness of the device;
    b. how the device is being used (on label or off label);
    c. if the device is or is not commercially available;
    d. if the device is or is not approved by the FDA;
    e. if the device is developed by the researcher; and
    f. if the device uses component parts that are FDA approved or developed by the researcher.
2. The principal investigator must include the IDE number in the IRB application through one of the following means:
    a. written communication from the sponsor;
    b. written communication from the FDA (this is required for investigator-held IDE); or
    c. sponsor protocol imprinted with the FDA's IDE number.
3. IRB staff will validate the IDE number with the FDA so that no further IDE determination will be required.
4. The study, if a clinical trial, must follow the NC State University IRB unit standard on clinical trials (Word document).

20.3.d.ii. Studies that qualify for an abbreviated IDE

1. The NC State University IRB application must:
    a. include the sponsor's/investigator's risk determination and justification of the device as NSR;
    b. state that the research team will comply with prohibitions against promotion as outlined in the Code of Federal Regulations 21 CFR 812.7 (opens in a new window);
    c. detail how the study will be monitored for participant protections; and
    d. detail how records and reports will be maintained.
2. The informed consent must:
    a. be physically signed unless the requirement for the documentation of consent has been waived in accordance with the Code of Federal Regulations 45 CFR 46.117 (opens in a new window);

b. include information about the study as one with an investigational device with an NSR determination;
c. disclose that representatives of the University, research sponsors, and/or government agencies, such as the FDA, may review research records (NC State IRB non-exempt consent template (Word document) has sample language for researcher to customize for their protocol); and
d. if relevant to the study, discuss the clinical trial nature of the study and federal requirements to post study information and de-identified results on http://www.clinicaltrials.gov (opens in a new window).

3. Once the study is approved by the convened IRB full board, the investigator can request a formal approval letter on letterhead that includes information the study as one with an investigational device with an NSR determination.
4. After the study is approved by the convened IRB full board and if it qualifies as a clinical trial, the research team must follow the NC State University IRB unit standard on clinical trial (Word document).

20.3.d.iii. Studies that are exempt from IDE requirements

1. The principal investigator will make the initial determination if the device is exempt from IDE requirements.
2. The investigator will provide the IRB a justification for the device as an NSR device.
3. The NC State University IRB will review the study in accordance with the Code of Federal Regulations 45 CFR 46 (opens in a new window) but the IRB will not make a SR or NSR determination for the device(s) being used in the study
4. After the study is approved by the IRB and qualified as a clinical trial, the research team must follow the NC State University IRB unit standard on clinical trials (Word document).

20.3.e. IRB Review and Approval

1. The NC State University convened IRB full board will document the decision points regarding whether a protocol requires an IDE, an abbreviated IDE, or is exempt from the IDE regulations.
2. If the study isn't exempt from the IDE regulations, the convened IRB full board will document the decision points regarding a SR or NSR determination for each medical device used in a study
3. The IRB will review a medical device study at the mid-level (e.g., expedited) if:
   a. the device usage poses no more than minimal risk to the subjects
   b. an IDE application is not required (refer to the Code of Federal Regulations 21 CFR 812 (opens in a new window))
   c. the device is cleared and approved by the FDA for marketing

d. the device will be used in accordance with its cleared and approved FDA labeling
e. the device usage can fit into a federally defined expedited category (please refer to the list of expedited review categories – opens in a new window)
    i. for device usage to be reviewed within the expedited 1 category, an IDE is not required OR the device has already been cleared and approved by the FDA for marketing and is being used in accordance with its cleared/approved labeling
    ii. for device usage to be reviewed within the expedited 4 category, the medical device must be cleared and approved by the FDA for marketing --if the study is using a cleared device for new indications or evaluating the device's safety or effectiveness, the study is not eligible for expedited review.
    iii. If an unapproved device is used as a tool, is minimal risk, and the study is not evaluating the device's safety or effectiveness, it can be reviewed under expedited category 4.

20.3.f. FDA Consultation

The NC State University IRB may contact or require the principal investigator to contact the FDA for an IDE determination. The FDA recommends that the sponsor/principal investigator contact the Center for Devices and Radiological Health (CDRH) (opens in a new window) to ascertain if a protocol is exempt from IDE requirements. Information about the IDE approval process can be found on the FDA's IDE Approval Process webpage (opens in a new window). A research team can submit a "Q-Submission" for a study risk determination by the FDA for whether a planned medical device clinical study is significant risk (SR), nonsignificant risk (NSR), or exempt from IDE regulations as defined in 21 CFR part 812 (opens in a new window). Further information about the Q-Submission process can be found on the FDA's Medical Device Submissions: The Q-Submission Program webpage (opens in a new window)

20.3.g. Combination Products

A combination product comprises two or more FDA-regulated components (i.e., drug/device, biologic/device, drug/biologic). The FDA considers the whole combination when determining the need for Investigational New Drug (IND) or IDE application. An application may be indicated if one part of the combination device is new, increases the risk(s) of an FDA-approved device/drug, or presents new risk(s) with the combined components previously approved for different indications. More information can be found on the FDA's Office of Combination Products website (opens in a new window).

20.3.h. Expanded Access

The FDA may permit the use of an investigational device for treatment with a patient with an immediately life-threatening disease or condition outside of clinical trials when no comparable or satisfactory alternative therapy options are available. Immediately life-threatening disease or condition is defined as a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment (21 CFR 312.300 – opens in a new window). The criteria for expanded access encompasses a situation where **all** of the following is present:

1. Patient has a serious or immediately life-threatening disease or condition
2. There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition
3. Patient enrollment in a clinical trial is not possible
4. Potential patient benefit justifies the potential risks of treatment
5. Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for treatment indication.

Investigators must contact the FDA to discuss "expanded access" using an investigational device outside of an IRB approved protocol. During weekdays (Monday through Friday, 8am to 4pm), researchers should contact CDRH's Division of Industry and Consumer Education at 301-796-7100 or DICE@fda.hhs.gov. For inquiries after hours or on the weekend, contact the FDA's Emergency Call Center at 866-300-4374. Note that ANY changes, including expanded access, to an IRB approved protocol requires an approved amendment before commencement of use.

20.3.i. Mobile Applications

Many software applications intended for use on mobile platforms are not considered medical devices. Some mobile apps can meet the definition of a medical device, and, depending on the potential risk to the subjects, may be regulated by the FDA. A good information resource is the FDA's Device Software Functions Including Mobile Medical Applications webpage (opens in a new window).

20.3.j. Human Subjects Research Training

All research personnel involved in a research study using a medical device with human subjects where the individual is interacting with participants via recruitment and consent, data collection, or analyzing identifiable private data, must successfully complete human subjects research training. NC State University's human subjects research training requirements (Word document) is listed on the IRB website. Note that some sponsors/funders such as the Department of Defense (DoD), FDA, National Institutes of Health (NIH), and National Science Foundation (NSF) may require additional human subjects research training beyond what the NC State IRB requires. It is the responsibility

of the principal investigator, not the IRB office, to ensure that human subjects research training is complete for all members of the research team.

Appendix A

Additional Documents for Submission and Resources

Submit with the IRB Application for Studies with a Medical Device

Medical Devices Used in Research Form (Word document)

- This form documents the risk assessment and should be completed by the sponsor or, if no project sponsor exists, the principal investigator.
- Complete this form for each device in the protocol that is being tested for safety and/or efficacy.
- The form should be submitted to the IRB office with the initial IRB application or with an amendment request where the device is being added to an approved study.
- Although a separate form needs to be submitted for each medical device being tested for safety and/or efficacy, each individual form should discuss all devices being studied for safety and efficacy as it is considered supplemental information to the IRB application.

NC State IRB Guidance and Reference Documents

- Biomedical Engineering (BME) Joint Department with UNC-Chapel Hill Specific Guidance
  - Directions for IRB Review, Approval, and Reliance Agreements (Word document)
  - BME IRB Procedures Template (Word document)
  - IRB Review and Approval for Research Involving Human Subjects from the Joint Department of Biomedical Engineering (BME) (Word document)
- Data Use Agreement (DUA) Guidance (opens in a new window)
- IRB Concerns Related to Data Security (Word document)
- Use of Applications and Software in Research with Human Subjects (Google document)

Educational Resources

- Duke University
  - Office of Regulatory Affairs and Quality (ORAQ) Education and Training (opens in a new window)
- Food and Drug Administration (FDA)
  - CDRH Learn (opens in a new window)
  - Device Advice: Comprehensive Regulatory Assistance (opens in a new window)
  - Device Software Functions Including Mobile Medical Applications (opens in a new window)
  - Digital Health Innovation Action Plan (opens in a new window)
  - Digital Health Software Pre-Cert Pilot Program (opens in a new window)
  - General Wellness: Policy for Low Risk Devices (opens in a new window)

    - Medical Devices (opens in a new window)
    - Medical Device Webinars and Stakeholder Calls (opens in a new window)
- Regulatory Guidance for Academic Research of Drugs and Devices (ReGARRD)
    - Investigational Device Exemption (opens in a new window)
    - Helpful Links (opens in a new window)

Appendix B

Definitions of Terms

Investigational Device
Investigational device is a tool, either stand alone or transitional, that is the object of an investigation. Information about the investigational device approval process (opens in a new window) can be found on the FDA's website.

Investigational Device Exemption (IDE)
IDE refers to the regulations under 21 CFR 812 (opens in a new window). An investigational device exemption (IDE) allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

Implant
A device that is placed into a surgically or naturally formed cavity of the human body if it is intended to remain there for a period of 30 days or more. The FDA may, to protect public health, determine that devices placed in subjects for shorter periods are also implants.

Label
A display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper. Refer to Device Labeling (opens in a new window)

Medical Device Accessory
An accessory is a finished device that is intended to support, supplement, and/or augment the performance of one or more parent devices. A parent device is a finished device whose performance is supported, supplemented, and/or augmented by one or more accessories. If labeling, promotional materials, or other evidence of intended use demonstrates that the device is intended to support, supplement, and/or augment another device, whether a particular brand or a device type, that device is considered an accessory.

Mobile Platform
A mobile platform is a commercial off-the-shelf (COTS) computing platform, with or without wireless connectivity, that is handheld in nature. Examples of mobile platforms include computers such as smart phones, tablet computers, or other portable computers.

Mobile Application
A mobile application or “mobile app” is a software application that can be executed (run) on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity), or a web-based software application that is tailored to a mobile platform but is executed on a server.

Mobile Medical Application (mobile medical app)
A mobile medical app incorporates device software functionality that meets the definition of device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); and either is intended to be used as an accessory to a, FDA regulated medical device; or to transform a mobile platform into an FDA regulated medical device.

Monitor
When used as a noun, an individual designated by a sponsor or contract research organization to oversee the progress of an investigation. The monitor may be an employee of a sponsor or a consultant to the sponsor, or an employee of or consultant to a contract research organization. Monitor, when used as a verb, means to oversee an investigation.

Noninvasive
When applied to a diagnostic device or procedure, means one that does not by design or intention:

- Penetrate or pierce the skin or mucous membranes of the body, the ocular cavity, or the urethra, or
- enter the ear beyond the external auditory canal, the nose beyond the nares, the mouth beyond the pharynx, the anal canal beyond the rectum, or the vagina beyond the cervical os.

Blood sampling that involves simple venipuncture is considered noninvasive, and the use of surplus samples of body fluids or tissues that are left over from samples taken for non-investigational purposes is also considered noninvasive.

Regulated Medical Device
A product that meets the definition of device in section 201(h) of the FD&C Act and that has been cleared or approved by the FDA review of a premarket submission or otherwise classified by the FDA. This definition can include novel devices, whether or not on a mobile platform, that the FDA will clear or approve by the review of a premarket submission or otherwise classify.

Transitional Device
A device subject to section 520(l) of the FD&C Act (opens in a new window) that the FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.