

Research Involving Medical Devices

1.0 Purpose

The purpose of this policy is to ensure compliance with all Food and Drug Administration (FDA) investigational device regulations by defining investigator and institutional responsibilities and by establishing procedures for the proper review, control, storage, use and handling of these devices.

2.0 Scope

At Wright State University (Wright State), all human research studies involving medical devices must be reviewed by an IRB of record and conducted in compliance with Investigational Device Exemption (IDE) requirements (21 CFR 812) unless determined to be exempt via 21 CFR 812.2(c).

This policy also applies to research involving medical devices in which the Wright State Institutional Review Board (hereafter referred to as IRB) acts as an IRB of record for an external institution (e.g., Premier Hospitals, Dayton VA, etc.).

3.0 Definitions

3.1 **Investigational Device** means a device, including a transitional device, that is the object of an investigation.

3.2 **Medical Device** means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them;
- 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;
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

3.3 **Significant Risk (SR) Device** means 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;

- Is purported or represented to be for a 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.
- 3.4 **Non-Significant Risk (NSR) Device** means a device that does not meet the definition of a SR device. Note that “non-significant risk” and “minimal” risk are not synonymous.
- 3.5 **Category A Device** means an experimental/investigational device for which there is no Medicare coverage.
- 3.6 **Category B Device** means a non-experimental investigational device that is eligible for Medicare coverage.
- 3.7 **510(k) Device** means a new device that the FDA agrees is substantially equivalent to a device already on the market. 510(K) devices can be marketed without clinical testing. However, if clinical data are necessary to demonstrate substantial equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations.
- 3.8 **Investigational Device Exemption (IDE)** means a submission to the FDA that allows the investigational device to be used in a clinical trial in order to collect safety and effectiveness data required to support a Premarket Approval Application (PMA). All clinical evaluations of investigational devices must have an approved IDE before the study is initiated.
- 3.9 **IDE Number** means the FDA assigned special identifier that corresponds to each device granted an IDE.
- 3.10 **Sponsor** means a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.
- 3.11 **Sponsor-Investigator** means an individual who both initiates and actually conducts, alone or with others, an investigation, that is, under whose immediate direction the investigational device is administered, dispensed, or used. The term does not include

any person other than an individual. The obligations of a sponsor-investigator under this policy include those of an investigator and those of a sponsor. Sponsor-investigators responsibilities include the following:

- Maintaining the Investigational Device Exemption (IDE)
- Obtaining qualified investigators and monitors
- Providing necessary information and training for investigators
- Monitoring the investigation
- Controlling the investigational device
- Reporting significant adverse events to FDA/investigators
- Maintaining and retaining accurate records
- Implementing and maintain quality assurance with written standard operating procedures.

At Wright State, any investigator who wishes to assume the role of a sponsor-investigator must first consult with the Office of the Vice President for Research to assess the proposed research plan and expertise/resources available to comply with “sponsor” requirements above.

- 3.12 **Transitional Device** means a device subject to section 520(1) of the FD&C Act and which the FDA previously regulated as a new drug or an antibiotic drug before May 28, 1976.
- 3.13 **Implant** means a device that is placed into a surgically or naturally formed cavity of the human body and is intended to remain there for a period of 30 days or more. To protect the public health, the FDA may determine a device placed in a subject for shorter periods is also an implant.
- 3.14 **Unanticipated Adverse Device Effect** means any serious adverse effect on health, safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application. Or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

4.0 **Policy**

This policy defines the applicability of federal regulations for medical devices and the procedures the IRB follows to determine whether a:

- 4.1 Study meets one of the exemption criteria defined in Section 5.1
- 4.1.1 Study involves a non-significant risk (NSR) device and can be conducted under an Abbreviated IDE, or
 - 4.1.2 Study involves a significant risk device (SR) and must be conducted under formal IDE submitted to and approved by FDA as defined by 21 CFR 812.

When submitting a new study involving an *investigational* device via the electronic submission system, a subset of questions regarding the device must be completed in the Initial Review Request. This information (including the device manual, reports of prior investigations conducted with the device, the proposed investigational plan, monitoring procedures, a risk assessment and the rationale used in making the device risk determination) is needed to provide the IRB with adequate information to determine whether the study is exempt from IDE requirements or involves an NSR or SR device.

It is important to understand the difference between research involving marketed devices versus investigational devices. Research involving a marketed device that is only being used to 1) measure a clinical outcome for medical care or used to elicit a physiologic response unrelated to the device itself, and 2) collects no safety or effectiveness data about or on the marketed device is not subject to this policy or FDA IDE regulations. For example, a study that uses an MRI to measure tumor growth but does not collect data on or assess how effective the MRI is at making the measurement.

This policy does not cover activities involving Humanitarian Use Devices. Investigators must follow the IRB's *Humanitarian Use Device Policy* in those cases.

5.0 Procedure

5.1 Exempt Determinations

There are five device exemption categories that may be applied to clinical research studies. It is important to understand that these exemptions apply only so long as study investigators remain qualified to conduct the research (see 21 CFR 812.119 for more information regarding *Disqualification*). If the IRB grants an exemption, it means that the study does not require an Investigational Device Exemption (IDE). It does not mean that the study is “exempt” from IRB review per 45 CFR 46.101(b).

If the PI believes the study involves an “exempt” device, he/she must indicate which of the following five exemption categories applies to the proposed study in the Initial Review Application:

- 5.1.1 Devices, other than transitional devices, in commercial distribution prior to May 28, 1976 when used or investigated in accordance with labeling in effect at that time;
- 5.1.2 Devices, other than transitional devices, introduced into commercial distribution on or after May 28, 1976, that the FDA determines to be substantially equivalent

to a device in commercial distribution prior to May 28, 1976, and which is used or investigated in accordance with approved labeling;

- 5.1.3 A diagnostic device (including in vitro diagnostic products in compliance with 21 CFR 809.10(c) if the testing:
 - 5.1.3.1 Is non-invasive
 - 5.1.3.2 Does not require an invasive sampling procedure that presents significant risk
 - 5.1.3.3 Does not by design or intention introduce energy into a subject, and
 - 5.1.3.3 Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- 5.1.4 Devices undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put the subject at risk, or
- 5.1.5 Custom devices, as defined by 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

The IRB will consider the information provided by the PI, sponsor, or FDA which indicates that the device meets one of the categories above. If the IRB agrees that the study is exempt from IDE requirements, the IRB does not need to make a SR/NSR determination and will evaluate the study in accordance with 21 CFR 50, 21 CFR 56, 45 CFR 46 and all applicable IRB policies and procedures. However, if unsure, the IRB may request that the PI consult with the FDA to verify that the study is exempt from IDE requirements.

5.2 Significant vs. Non-Significant Risk Determinations

Study sponsors are responsible for making the initial risk determination and presenting it to the IRB via the local PI. The IRB must review the sponsor's significant risk (SR) or non-significant risk (NSR) determination for every investigational medical device study and modify the determination if the IRB disagrees with the sponsor. **However, if the FDA has already made the determination for the study, the FDA's determination is final.**

To make a SR/NSR determination, the IRB will review information such as the sponsor's risk designation and justification, description of the device, reports of prior investigations, study protocol, and subject selection criteria at a convened meeting. If the PI requests a NSR determination, he/she will be required to provide additional

information via the initial application questions regarding why the investigational device does not meet the definition of a SR device (see Definitions above).

If the IRB determines that a study involves an NSR device, the IRB may then approve the study using standard approval criteria at 21 CFR 56.111. Once the study receives IRB approval the PI must still follow the abbreviated IDE requirements which include labeling, informed consent, monitoring, records, reports, and prohibition on promotion. However, investigators are not required to submit this information to the IRB. Only study progress and final reports are required to be submitted at the time of continuing review and study closure.

The IRB's risk determination for the device must be recorded in the minutes of the convened meeting and in written correspondence (e.g., study approval letter) with the PI. If the IRB disagrees with the sponsor's NSR assessment and decides that the study is SR, the IRB will document this determination, and where appropriate, inform the sponsor per 21 CFR 812.66. The IRB may also vote to allow continuing review to be conducted using the expedited review procedure if the research poses no more than minimal risk to subjects and no additional risks have been identified.

5.3 Significant Risk Device Requirements

Studies involving an investigational medical device determined to represent a significant risk (SR) may not proceed without submission of an Investigational Device Exemption (IDE) application to the FDA and subsequent receipt of confirmation of the FDA decision on the application. The term "exemption" in this case means exempt from laws prohibiting unapproved products to move in interstate commerce. It does not mean that the study is "exempt" from IRB review per 45 CFR 46.101(b).

The IDE allows the investigational medical device to be used in a clinical study to collect safety and efficacy data required to support a marketing application. An IDE may be held either by a commercial sponsor/institution (e.g., Medtronic or Johns Hopkins University) or by a sponsor-investigator.

Research involving SR devices must be reviewed and approved at a convened meeting. For studies involving SR devices where the PI is not the sponsor, the PI must provide the IRB at the time of his/her initial IRB submission with the IDE number and one of the following three documents to validate the IDE:

- 5.3.1 Written communication from the sponsor;
- 5.3.2 Written communication from the FDA (required for investigator-held IDE);
- 5.3.3 Sponsor protocol imprinted with IDE number.

5.4 Reporting Deviations and Unanticipated Adverse Device Effects

For device studies under the oversight of the IRB, reporting must be in compliance with the *Reportable Problems or Events Policy*. Investigators must understand that FDA device regulations at 21 CFR 812.150(a)(4) require prior approval from the sponsor of all planned deviations, including minor deviations. Planned deviations requested of a sponsor must be submitted for review and approved by the IRB prior to instituting any IDE research planned deviations. The PI must submit an Amendment form in the IRB electronic submission system and keep on file a copy of the written approval document from the sponsor when a deviation is granted.

For device studies under the oversight of another IRB of record, the PI is responsible for ensuring that all study investigators are aware of and understand the reporting requirements for that device study before it is initiated.

5.5 Expanded Access and Emergency Use for Medical Devices

Expanded access is a potential pathway for patients with a serious or life-threatening disease or condition to access an investigational medical device that has not been approved or cleared by the FDA for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available. This access can occur via one of three FDA-approved mechanisms: 1) Emergency Use, 2) Non-Emergency Individual/Small Group Access, or 3) a Treatment Investigational Device Exemption (IDE).

5.5.1 Emergency Use

“Emergency use” means the use of an investigational medical device in an emergency situation. It is intended to provide patients and physicians with access to devices intended to treat life-threatening or serious diseases or conditions when there is no available alternative and no time to obtain FDA approval. “Emergency use” is not the same as “emergency research.” Emergency research is “planned research” conducted in emergent situations that is typically conducted without informed consent.

Treating physicians utilizing the IRB for emergency use review must follow the submission and review procedures found in the *Emergency Use Policy*.

Emergency use may apply even if the investigational device is being studied in a clinical trial under an IDE at Wright State or affiliated hospital. For example, if a Wright State/affiliated hospital treating physician (who is not a member of the

clinical research study team) needs to use the device in a manner inconsistent with the approved investigational plan or wishes to use the device to treat a patient with a life-threatening or serious disease or condition, he/she may do so under this regulatory provision with authorization from the device manufacturer.

Emergency use of an investigational device may occur before an IDE is approved and when a device is not being studied under an IDE given the following criteria:

- The patient has a life-threatening or serious disease or condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

It is important to note that for emergency use of investigational devices, prior FDA approval is not required. The FDA expects a treating physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. If a device is used in circumstances meeting the criteria listed above, the treating physician must follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

- Informed consent from the patient or a legally authorized representative;
- Clearance from the institution via the Institutional Official (IO) or Designee;
- Concurrence of the IRB chairperson; or
- An independent assessment from an uninvolved physician; and
- Authorization from the device manufacturer.

If there is an IDE for the device, the IDE sponsor, utilizing information provided to sponsor by the Wright State/affiliated hospital physician, must **notify the FDA of the emergency use within five days through submission of an IDE Report (§812.35(a)(2))**. This follow-up report should include a summary of the conditions constituting the emergency, the patient protection measures that were followed, and patient outcome information.

If no IDE exists, the treating physician should submit a follow-up report on the use of the device (description of device used, details of the case, and the patient protection measures that were followed) to:

Food and Drug Administration
Center for Devices and Radiological Health
10903 New Hampshire Ave
Document Control Center
WO66 Rm G-609
Silver Spring, MD 20993

The treating physician is also responsible for concurrently providing copies of all FDA reports described in this section to the IRB. The *Emergency Use Policy* includes detailed instructions regarding submissions and required reviews.

5.5.2 Non-Emergency Individual Patient/Small Group Access

This mechanism (frequently referred to as Compassionate Use) can be used for devices that are being studied in a clinical trial under an IDE for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating or diagnosing their disease or condition. It can also be used for devices that are not being studied in a clinical investigation (i.e., an IDE does not exist for the device). This mechanism is typically approved by the FDA for individual patients but may be approved to treat a small group, if the small group request is under an IDE.

Non-emergency individual patient access may be granted by the FDA under the following criteria:

- The patient has a life-threatening or serious disease or condition;
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and
- Potential patient benefit justifies the potential risks of the investigational device.

The FDA cannot require a device manufacturer to provide an investigational device for this use. However, if the device manufacturer agrees to provide the device to the treating physician for this use, there are two different processes to follow to obtain FDA approval depending on whether there is an IDE in place.

If an IDE already exists, the IDE sponsor must submit an IDE supplement to the FDA in accordance with current regulations.

If an IDE does not currently exist, a request for a single patient must be submitted to the FDA by the manufacturer or the treating physician that includes the following:

- A description of the patient's condition and the circumstances necessitating treatment;
- A discussion of why alternative therapies are unsatisfactory and why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;
- An identification of any deviation in the approved clinical protocol that may be needed to treat the patient;
- The patient protection measures that will be followed, including;
 - A draft of the informed consent document that will be used;
 - Written clearance letter from an appropriate official (hospital or university);
 - Written concurrence of the IRB Chairperson;
 - An independent assessment from an uninvolved physician and
 - Authorization from the device manufacturer on the use of the device.

Normally, the IRB will require documentation of FDA approval before issuing final approval. In such cases, the written request to the FDA should also indicate that IRB Chair concurrence will be obtained prior to the use of the device. In addition, if the request is for a few patients, it should include the total number of patients to be treated.

Before using the device, the treating physician must submit the following to the IRB via the electronic submission system (which can be initiated concurrently with FDA submission above):

- A new Initial Review Form with a completed device section ensuring that the study title includes: INDIVIDUAL EXPANDED ACCESS REQUEST
- Documentation of sponsor's authorization and FDA's concurrence with use (e.g., compassionate use IDE supplement approval letter from FDA)
- A brief description of patient(s) situation, treatment, and monitoring plan (e.g. a protocol that supplements the IDE)
- An independent assessment from an uninvolved physician, if available, and
- A copy of the informed consent form to be used.

The IRB will screen the submission to ensure completeness and assign the submission to the IRB Chair/Designee for review. Once the treating physician

receives written concurrence from the IRB Chair/Designee after FDA approval, he/she can obtain informed consent from the patient(s) or his/her legally authorized representative.

The treating physician should devise an appropriate schedule for monitoring the patient, taking into consideration the investigational nature of the device and the specific needs of the patient. The patient should be monitored to detect any possible problems arising from the use of the device.

Following the use of the device, a follow-up report should be submitted by whoever submitted the original individual patient/small group access request to the FDA within 45 days of using the investigational device. This report should present summary information regarding patient outcomes, including any safety related information.

At the conclusion of the Individual/small group treatment, the treating physician is responsible for providing the IRB with a summary of actual use and any safety related information or problems encountered as part of the Study Closure submission process. This includes a copy of the 45-day report submitted to the FDA. This submission will normally be reviewed by the convened IRB at its next regularly scheduled meeting.

5.5.3 Treatment Investigational Device Exemption (IDE)

For an investigational medical device, an approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggest that the device is effective, then the trial may be expanded under a new IDE, to include additional patients with life-threatening or serious diseases. This is called a Treatment IDE.

Use of a treatment IDE requires use of informed consent and prospective convened IRB review and approval in accordance with 21 CFR 56 and 21 CFR 50. investigators who want to pursue a treatment IDE must consult and follow applicable FDA guidance and regulations (21 CFR 812.36).

If investigational devices are going to be utilized under a Treatment IDE, the investigator must complete a new Initial Review Form including the device section via the electronic submission system. The application must contain the following information:

- Treatment IDE number
- Name of Treatment IDE holder/sponsor, and

- Copy of sponsor protocol imprinted with IDE number or written communication from FDA or sponsor documenting the Treatment IDE number.

The IRB must review and approve the application at a convened meeting before the device can be utilized at Wright State/affiliated hospitals.

5.6 Responsibilities

In accordance with FDA regulations 21 CFR 812 and Wright State policies, the sponsors and/or investigators are responsible for ensuring that an investigation is conducted according to the signed agreement and the investigational plan; for protecting the rights, safety, and welfare of subjects under the investigator's care; ensuring that informed consent is obtained; and for the proper ordering, handling, storage, and disposition of investigational devices in clinical trials at Wright State/affiliated hospital. If use of medical devices for research are not subject to site-specific hospital policies, investigators must ensure the following:

5.6.1 Ordering

- Ordering of an investigational device must be done by the Principal Investigator (PI) or designated study personnel according to the terms of the executed agreement and only after the protocol has been approved by the IRB.

5.6.2 Receipt

- Investigational devices may only be received by the PI or designated study personnel at a Wright State/affiliated hospital business address.

5.6.3 Storage/Labeling

- Investigational devices used in conjunction with a research protocol must be kept in a locked and secured area and must be labeled "Caution: Investigational Device-Limited by Federal Law (or United States Law) to Investigational Use."
- Access to investigational devices must be limited to the PI or designated study personnel.
- Study device supplies must be labeled as investigational by the manufacturer or PI (if not done by manufacturer) and maintained and stored separately in a secure location by research personnel.

5.6.4 Dispensing

- The investigational device may not be given to anyone not enrolled in the study.
- The PI must not supply the investigational device to any person not authorized.
- For accountability purposes, an investigational device accountability log(s) must be kept for all investigational device studies. Documentation of the following elements should be recorded for each device used:
 - The type of device
 - Model number
 - Serial number
 - Lot number (if applicable)
 - Date received
 - Research subject Initials or ID number (for internal tracking purposes)
 - Date implanted or used
 - Device return, repair, or destruction information
- Personnel may not remove any device(s) from a Wright State/affiliated hospital floor or department stock and substitute them for an investigational device, even if the device, under study, is approved and used in practice.
- If the sponsor provides an investigational device accountability log, study staff must review the log to determine if the required elements above are included. If the log provided by the sponsor does not include all the required elements, a separate log including those elements must be maintained.

5.6.5 Maintaining an Investigational Device Log(s):

- Investigational device logs must be maintained by the study team and stored long term in the study's regulatory binder for the period required by the federal regulations or terms of the agreement, whichever is longer.
- The full names, titles/positions, signatures and/or initials of all Wright State/affiliated hospital personnel responsible for maintaining or documenting in the log(s) must be indicated on either the Delegation of Authority Log or in the investigational device log itself.
- The PI or designated study personnel must regularly review the device logs to ensure that there is an adequate number of devices or the appropriate type of devices available (sizes, etc.) to conduct the scheduled clinical trial procedures.

5.6.6 Disposition

- Upon conclusion or termination of the clinical investigation, or by the sponsor's request, the PI shall return to the sponsor any remaining supply of the device or otherwise dispose of the device(s) as the sponsor directs.

Investigational device(s) should not be destroyed by the PI or study personnel without obtaining advanced written permission from the sponsor.

- Study team must document the reason for disposition, timing of disposition and names of study personnel involved in disposition.
- In the event of research software, Wright State/affiliated hospital privacy/IT security officials must provide clearance for removal and disposition must include the date the software was deprogrammed or removed from the device(s).

5.6.7 Maintenance and Cleaning

- All investigational devices must be properly maintained and cleaned.

5.6.8 Reliance on External IRB of Record

- If relying on an IRB of Record other than the Wright State IRB, the PI is responsible for ensuring that all institutional approvals and agreements are in place prior to engaging in that reliance. This includes submitting an external reliance request via the IRB electronic submission system and receiving written confirmation from the Office of the Vice President for Research prior to commencing the research, unless conducted solely by affiliated hospitals. In such cases, PI must follow Premier/Dayton VAMC reliance policies and procedures.

6.0 Records:

All records related to this policy will be stored and maintained in accordance with any Wright State policy, federal regulations and sponsor requirements associated with the human subject research under review by the IRB.

7.0 References:

- 21 CFR 812
- 21 CFR 50
- 21 CFR 56
- 21 CFR 807
- 21 CFR 809.10
- VA Handbook 1108.04 and 1200.05
- 38 CFR 16
- FDA IDE Guidance:
<https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/investigationaldeviceexemptionide/ucm162453.htm>