



DOWNSTATE
HEALTH SCIENCES UNIVERSITY

IRB Member Orientation Session III

Presented by:

Nikol Celestine

Kevin Nellis

March 2022



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Risk Assessment

Risk Assessment

Minimal risk means that the **probability** and **magnitude** of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in **daily life** or during the performance of **routine physical or psychological examinations or tests**.

- (a) Calibrated to the life of normal, healthy individuals and daily life to be those activities to which most individuals are exposed.
- (b) IRB may determine some risks constitute greater than minimal risk for populations that are vulnerable by virtue of their condition or circumstances.

Risk Assessment

Which studies are no greater than minimal risk? Why?

Survey for individuals with traumatic experiences.

A cardiologist enrolls diabetic patients into an exercise study using a weight supported treadmill. A crash cart is available to mitigate risk of cardiac arrest.

A study to evaluate vitamin D3 (prescription dose) in children scheduled to undergo standard of care hematopoietic stem cell transplants for AML. The outcome measures are incidence of GVHD, infection rates, and overall survival.

Research with adults that collects 2 mls of blood for genetic testing and takes a single chest x-ray.

Criteria and Considerations for IRB Approval

Criteria for IRB Approval of (non-exempt) Research (1)

45 CFR 46.111

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized:

- (i) By using **procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk**, and
- (ii) Whenever appropriate, **by using procedures already being performed on the subjects for diagnostic or treatment purposes**.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, [§46.116](#).

(5) Informed consent will be appropriately documented or appropriately waived in accordance with [§46.117](#).

Criteria for IRB Approval of (non-exempt) Research (2)

45 CFR 46.111

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

(7) When appropriate, there are **adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data**.

(i) The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.

(8) For purposes of conducting the limited IRB review required by [§46.104\(d\)\(7\)](#), the IRB need not make the determinations at paragraphs [\(a\)\(1\)](#) through [\(7\)](#) of this section, and shall make the following determinations:

(i) *Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of [§46.116\(a\)\(1\)-\(4\)](#), [\(a\)\(6\)](#), and [\(d\)](#);

(ii) *Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with [§46.117](#); and

(iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

**Note: Downstate has not implemented the Broad consent regulations.*

Additional Criteria and Considerations for IRB Approval of (Non-Exempt) Research

Follow IRB Guidance and Policy IRB-01, for an extensive list of criteria and considerations.

Follow FDA regulations for clinical investigations.

When vulnerable populations are included, the IRB must also ensure the research is in compliance with regulations to the extent required by 45 CFR 46, subpart B (Pregnant Persons, Human Fetuses, and Neonates), C (Prisoners), and D (Children).

For FDA regulated clinical investigations involving children, ensure compliance with 21 CFR 50, subpart D.

Each Federal Agency has additional requirements.

For clinical trials which follow ICH-GCP requirements, the IRB must ensure additional requirements are met.

Categories of Permissible Research Involving Children (1)

Category	Evaluation	Requirements
<p>Category 404 (45 CFR 46.404 and 21 CFR 50.51)</p>	<ul style="list-style-type: none"> ✓ No greater than minimal risk 	<ul style="list-style-type: none"> ✓ Permission of one parent/legal guardian ✓ Assent
<p>Category 405 (45 CFR 46.405 and 21 CFR 50.52)</p>	<ul style="list-style-type: none"> ✓ Greater than minimal risk ✓ Presents prospect of direct benefit to the individual research participants ✓ The risk is justified by the anticipated benefit to the participants; and ✓ The relation of the anticipated benefit to the risk is at least as favorable to the participants as that presented by available alternative approaches. 	<ul style="list-style-type: none"> ✓ Permission of one parent/legal guardian ✓ Assent

Categories of Permissible Research Involving Children (2)

Category	Evaluation	Requirements
<p>Category 406 (45 CFR 46.406 and 21 CFR 50.53)</p>	<ul style="list-style-type: none"> ✓ Greater than minimal risk ✓ Minor increase over minimal risk ✓ No prospect of direct benefit to the individual research participants ✓ Likely to yield generalizable knowledge about the research participants' disorder or condition ✓ Intervention/procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations 	<ul style="list-style-type: none"> ✓ Permission must be obtained by both parents (or legal guardians), unless one is deceased, unknown, incompetent or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child ✓ Assent ✓ If children are wards of the state or any other agency, institution, or entity are included, additional requirements of 45 CFR 46.409 must also be met.
<p>Category 407 (45 CFR 46.407 and 21 CFR 50.54)</p>	<ul style="list-style-type: none"> ✓ Research is not otherwise in category 404, 405, or 406, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. 	<ul style="list-style-type: none"> ✓ Includes 406 requirements ✓ OHRP (or by the FDA, if FDA regulated) must also approve the research

Which category of permissible research with children applies to each of the following studies?

Examples:

STUDY #1: Vaccine hesitancy survey of middle school students. (404)

STUDY #2: Pediatric clinical trial with an investigational agent that is compared to standard of care control arm. Pre-Clinical trials indicate a possible direct benefit of the agent. (405)

STUDY #3: Pediatric clinical trial that compares effectiveness of a new route for an anti-seizure medication. Study is a cross-over study comparing rectal gel to an investigational nasal spray. All subjects have refractory epilepsy. (406)

STUDY #4: Pediatric clinical trial to evaluate the safety and effectiveness of an investigational drug in response to the COVID-19 pandemic. (possibly 407?)

Clinical Trials with Investigational Drug or Biologics

In general, an IND (Investigational New Drug Application with the FDA) is required for clinical trials with:

- Investigational drugs or biologics
- FDA approved drug/biologic, unless exempt from IND
- Some studies using endogenous compounds, live organisms, cosmetics, dietary supplements, food, food-derived products, spices, herbs, or electronic cigarettes

IRB application requirements for studies with IND:

- IND Letter from FDA or Sponsor
- FDA Statement of Investigator (FDA Form 1572)
- Investigator's Brochure

References:

FDA Guidance on INDs – Determining Whether Human research Studies Can Be Conducted Without an IND

FAQs - Clinical Studies Involving Electronic Cigarettes and INDs

Criteria for IND Exemption

Full text for IND exemption criteria is available at [21 CFR 312.2\(b\)\(2\)\(ii\)](#)

Not intended to be reported to FDA;

Not to support change advertising of FDA approved product;

Does not involve change in route, dosage, patient population, or other factor that significantly increases the risks of FDA approved drug; and,

IRB approves study and informed consent

Medical Device Studies

Reference: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126418.pdf>

Is an IDE needed?

- If study evaluates safety and effectiveness of a medical device, determine first if it meets criteria for IDE exemption at 21 CFR 812.2(c).
- If not exempt, determine if study is Significant Risk (SR) or Non-Significant Risk (NSR) device study.
- If SR, an IDE is needed from FDA

What is a SR Device Study?

- Medical device is an implant;
- Presents a potential for serious risk to the health, safety, or welfare of a research participant;
- Supports or sustains life;
- Substantially important in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health; or
- Otherwise presents a potential for serious risk to the health, safety, or welfare of a research participant.

What is a NSR Device Study?

- Medical device study that is not a SR study

IDE Exemption [21 CFR 812.2(c)]

Reference: [Frequently Asked Questions About Medical Devices | FDA](#)

In accordance with 21 CFR 812.2(b), sponsors and investigators of certain studies are exempt from the requirements of 21 CFR Part 812, with the exception of §812.119 (disqualification of a clinical investigator). Examples of exempt studies are consumer preference testing, testing of a device modification, or testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data, or put subjects at risk.

Studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling are exempt from Part 812.5 Note: Studies of a cleared device *for a new use* must comply with the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations. Similarly, studies of a PMA approved device are exempt from the IDE requirements if the device is being studied for the indications in the approved labeling.

In addition, diagnostic device studies (e.g., *in vitro* diagnostic studies) are exempt from the requirements of 21 CFR Part 812 under certain circumstances. The study is exempt as long as the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. 21 CFR 812.2(c)(3).

Medical Device Quiz

Determine whether each is a medical device study. If so, determine if the study is exempt from IDE requirements, or whether it is NSR or SR:

Examples:

STUDY #1: A clinical investigation that evaluates the safety and effectiveness of a new implantable cardiac defibrillator to prevent heart failure. (SR)

STUDY #2: A study that evaluates whether wooden tongue depressors are better than plastic tongue depressors. (Exempt)

STUDY #3: A study to evaluate whether an Endopap device can predict vascular problems in patients with sickle cell anemia. (Exempt)

STUDY #4: A clinical trial for FDA market approval of a new diagnostic test and there is no gold standard to confirm the test results. (NSR)

IRB Actions

IRB Actions

Full and expedited review

Approve

Approve with conditions

- Response reviewed by expedited review

Require modifications to secure approval

- Response reviewed by Full Board, if initial review was required by Full Board

Disapprove

Note: An IRB member may also refer an exempt or expedited review to the full board.

Conditional Approval

Federal Guidance: [OHRP Guidance](#) & [FDA Guidance](#)

Specific changes are required (usually minor)

IRB notifies the PI in writing of the changes that are required.

The IRB may approve research with conditions if:

- Given the scope and nature of the required conditions, the IRB is able to make all of the determinations required for approval
-AND-
- IRB assumes the conditions will be satisfied

Examples of Conditional Approval

Confirmation of specific understandings on the part of the IRB regarding how the research will be conducted (e.g., confirmation that the research excludes children);

Submission of additional documentation (e.g., certificate of CITI training);

Precise language changes to protocol or informed consent documents; or

Substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

Circumstances that Preclude IRB from Approving Research

IRB cannot make one or more of the determinations required for approval (e.g., 111 findings or subpart findings)

Example:

- IRB is unable to make the required determinations about risks and benefits, adequacy of privacy and confidentiality protections, or adequacy of informed consent because insufficient information is provided
- -AND-
- the IRB is unable to specify changes that would allow the IRB to make these determinations.

Circumstances Which Preclude the IRB from Granting Conditional Approval

EXAMPLES:

- A. Justification for using a placebo or withholding available treatment for a serious medical condition
- B. Providing a justification for enrolling children and how regulatory requirements are met
- C. Revising a study hypothesis
- D. Providing a description of procedures that the control group will undergo
- E. Clarifying information regarding risks
- F. Clarifying timing or circumstances for seeking informed consent
- G. Providing additional monitoring plans



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Thank You!