

University of Rochester	Office for Human Subject Protection		
	Research Subjects Review Board		Effective Date: 11/27/2019
	Research Involving FDA Regulated Drugs, Biologics, and Supplements		Policy 605

POLICY

1. Purpose

Outline the responsibilities and regulatory requirements when conducting human subject research that involves the use of drugs, agents, biological products, or nutritional products (e.g., dietary supplements) under the oversight of the Food and Drug Administration (FDA).

2. Scope

This policy applies to human subject research conducted or supported by employees or agents of the University of Rochester that involves the use of FDA regulated products.

3. Definitions

3.1. *Clinical Investigation* – Any experiment in which a drug is administered or dispensed to, or used, involving one or more human subjects (i.e., an experiment is any use of an approved or unapproved drug, except for the use of a marketed drug in the course of medical practice). A “marketed drug” is a drug that has been approved by the FDA and cleared for sale.

3.2. *Dietary Supplement* – A product taken by mouth that is intended to supplement the diet and contains one or more dietary ingredients (e.g., vitamins, minerals, herbs, amino acids, extracts, combinations of preceding examples).

3.3. *Drug* – Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and articles (other than food) intended to affect the structure or function of the body.

3.4. *Investigational Drug* – A new drug or biological drug that is used in a clinical investigation. Also includes a biological product this is used in vitro for diagnostic purposes. Examples of types of studies where an investigational drug is used includes:

- a) A drug in any of the clinical stages of evaluation (i.e., Phase 1, 2, 3), which has not been approved by the FDA for general use or cleared for sale in interstate commerce.
- b) A marketed drug involved in a post-marketing surveillance (i.e., Phase 4) study.
- c) A marketed drug proposed for a new use.
- d) A marketed drug to be used in new dosage form or method of administration.
- e) A marketed drug that contains a new component.
- f) A new combination of two or more marketed drugs.
- g) A combination of marketed drugs in new proportions.

3.5. *Investigational New Drug Application (IND)* – A request for FDA authorization to administer an investigational drug to humans. If required, such authorization must be

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secured before RSRB approval of the research study, and prior to interstate shipment and administration of the investigational drug.

- 3.6. *Commercially Sponsored IND* – An IND submitted primarily by a company to conduct a clinical trial with the goal to obtain marketing approval for a new product.
- 3.7. *Expanded Access* – A mechanism within the FDA IND regulations for allowing use of investigational and approved drugs for patients with life-threatening or serious diseases or conditions when there is no comparable or satisfactory alternative therapy, for the primary purpose of diagnosing, monitoring, or treating a patient’s disease or condition.
- 3.8. *Emergency Use IND* – A type of expanded access where the FDA issues authorization to ship and allow use of an investigational drug or biologic for the treatment of one patient or patients and there is not time for submission and review of a regular IND or for convened RSRB review.
- 3.9. *Treatment IND* – A type of expanded access where an IND is obtained as a mechanism for providing patients not in a clinical investigation with investigational drugs. A treatment IND may be granted once sufficient data have been presented to show the drug may be effective and does not have unreasonable risks.
- 3.10. *Open Label IND* – A mechanism for carrying out a study to obtain additional safety data once the controlled study has ended to provide continued treatment so subjects may receive the benefits of the investigational drug until marketing approval is obtained.
- 3.11. *Group C Treatment IND* – Under agreement between FDA and the National Cancer Institute (NCI), a mechanism for distribution of an investigational agent to oncologists for treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are distributed only by the National Institutes of Health (NIH) under NCI protocols.
- 3.12. *Immediately Life Threatening Disease or Condition* – 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 (i.e., the patient has a disease or condition that causes major irreversible morbidity or the patient is in the stage of disease that requires intervention before review at a convened meeting of the IRB is feasible).
- 3.13. *Serious Disease or Condition* – A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical

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judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

- 3.14. *Phase 1 Clinical Trial* – The initial introduction of an investigational new drug into humans. These studies are closely monitored and are usually conducted in healthy human volunteers and are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. These studies also evaluate drug metabolism, structure-activity relationships, and the mechanism of action in humans. Assessment of safety and adverse events is the primary objective.
- 3.15. *Phase 2 Clinical Trial* – Early controlled clinical studies conducted to obtain preliminary data on the effectiveness of the drug for a particular indication(s) in patients with the disease or condition. This phase also helps determine the common short-term side effects and risks associated with the drug, and may be conducted to determine optimal drug dosing.
- 3.16. *Phase 3 Clinical Trial* – Intended to gather the additional information about effectiveness and safety needed to evaluate the overall risk-benefit relationship of the drug. These studies also provide an adequate basis for providing information to the general population about the drug and for development of information for physician labeling.
- 3.17. *Phase 4 Clinical Trial* – Post-marketing studies of an FDA-approved drug in order to gain more information (e.g., to further study the incidence of a specific adverse reaction or the long-term effects of the drug on morbidity and mortality). Studies may include, for example, evaluation of different dosages or schedules of administration, use of the drug in other stages of the disease, use of the drug over a longer period of time, or, if approved for use in adults, use of the drug in a pediatric population.
- 3.18. *Sponsor* – An entity who takes responsibility for and initiates a clinical investigation regardless of financial support, and may be an individual, company, governmental agency, academic institution, private organization, or other organization. This entity does not actually conduct the clinical investigation, unless the entity is a Sponsor-Investigator.
- 3.19. *Sponsor-Investigator* (or Investigator-held IND) – An Investigator who is responsible for the initiation and conduct of a clinical investigation, as well as the responsibility for the direct oversight of the administration, dispensing and/or use of the test item across all sites (e.g., regulatory Sponsor). For example, when a physician submits an IND

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application to the FDA to propose a study of an unapproved product or of an approved product for a new indication or in a new patient population.

3.20. *Test Article* - Any drug or biologic for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the Food, Drug and Cosmetics Act or under sections 351 or 354-360F of the Public Health Service Act.

4. References

- 4.1. FDA 21 CFR 50; FDA 21 CFR 56; FDA 21 CFR 312; FDA 57 FR 13250
Treatment Use of Investigational Drugs” FDA Information Sheet;
FDA Guidance “Investigational New Drug Applications – Determining Whether Human Research Studies Can Be Conducted Without an IND”;
FDA Guidance “IRB Responsibilities for Reviewing the Qualifications of Investigators, Adequacy of Research Sites, and the Determination of Whether an IND/IDE is Needed”
FDA Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers
- 4.2. [Policy 404 Criteria for Approval of Research](#);
[Policy 504 RSRB Reliance for Review](#);
[Policy 607 Emergency Use of Investigational Drugs, Biologics and Medical Devices](#);
[Policy 608 Research Involving Genetic Testing and Gene Transfer](#)
[Policy 901 Investigator Responsibilities](#)
- 4.3. [RSRB Treatment Use Protocol Template](#);
[RSRB Treatment Use Consent Template](#)

5. Responsibilities

- 5.1. In addition to the responsibilities indicated in *Policy 901 Investigator Responsibilities* “Requirements for Principal Investigators Conducting FDA Regulated Research”, Investigators conducting research involving investigational drugs, agents, biologics, or dietary supplements are responsible for providing the RSRB with all applicable information and documentation requested in the RSRB protocol template and the IRB review system, when the RSRB is the Reviewing IRB, including but not limited to the following, as applicable:
 - A plan for receipt, storage, handling, and dispensing of the investigational agent,
 - Investigator Brochure (or package insert),
 - If an IND application was submitted to the FDA, documentation from the FDA verifying the IND number and indicating the study is safe to proceed (e.g., the FDA letter assigning the IND number and safe to proceed letter). If the safe to proceed letter has not been received, the RSRB will accept documentation from the Sponsor or Investigator indicating the FDA’s confirmation that the study may proceed.

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- If the FDA has indicated the study is exempt, documentation from FDA confirming this determination.
- If an IND application was not submitted to the FDA and the Investigator is requesting the RSRB to confirm that the study is exempt from the IND regulations, justification written into the protocol as to why the use of the investigational drug in this application is exempt.
- If the UR Investigator is the Sponsor-Investigator, documentation of UR IND training certification.

5.1.1. When the Investigator is also the Sponsor-Investigator, the Investigator assumes additional responsibilities as stated in 21 CFR 312, including but not limited to:

- Submitting the IND application for FDA review,
- Complying with FDA regulatory reporting requirements including IND Safety reporting, Annual Reports, Final Study Report, and withdrawal or inactivation of the IND,
- Adhering to drug manufacturing and control standards,
- Assessing safety issues,
- If a multi-center study, ensuring IRB approval from each study site prior to shipping clinical supplies to the site,
- If a multi-center study, monitoring Investigators and keeping them informed of study related issues.

5.1.2. When the RSRB is the Relying IRB, Investigators are responsible for following the submission requirements of the Reviewing IRB as described in *Policy 504 RSRB Reliance for Review*, as well as any institutional requirements described within this policy.

5.2. When the RSRB is the Reviewing IRB, the RSRB is responsible for review and approval of research involving drugs, agents, biologics and dietary supplements under both the Department of Human Health and Services and FDA regulations. In addition to *Policy 404 Criteria for Approval of Research*, the following responsibilities for RSRB review of the research apply, as applicable:

5.2.1. Confirmation that one of the following is true:

- The product has an IND issued by the FDA, or
- The use of the product in the study meets all of the categories indicated in Section 7.1.

5.2.2. When an Investigator indicates that the use of the study drug is exempt from IND requirements, the board, or Chair for expedited review, will confirm that the Investigator's justification meets the criteria for exemption.

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6. Requirements for Research Use of Investigational Drugs, Agents, Biologics, Supplements

- 6.1. An IND is generally required for research involving a drug, biologic, dietary supplement, or other agent when all of the following apply:
- The research involves a “drug”,
 - The research is a “clinical investigation”,
 - Research of a product to develop information about the product’s safety or efficacy, including FDA approved drugs.
 - When the intent of the research is to generate data that will lead to a new advertising claim, a new clinical indication, or a new formulation of the product.
 - The clinical investigation is not exempt from the IND requirements [21 CFR 312.2(b)].
- 6.2. A study conducted to investigate a dietary supplement’s ability to diagnose, cure, mitigate, or prevent a disease, may require an IND under 21 CFR 312. The Investigator should consult the FDA for a determination of whether the supplement falls under the definition of “drug” and requires an IND to conduct the research.
- 6.3. For FDA-regulated research involving an investigational drug conducted outside of the United States, country law regarding investigational articles should be followed. An IND is not required provided the study is conducted in accordance with the Declaration of Helsinki (1989) and FDA Good Clinical Practice guidelines, and FDA is able to validate the data from the study through an onsite inspection, if FDA deems it necessary.
- 6.4. An investigational drug, agent, or biologic utilized in a clinical trial may be stored in an area other than the UR or its affiliated institutions if it is under the direct supervision of the Investigator and is maintained in a locked, secure location with access only by qualified research personnel, and with Sponsor approval when applicable. Information regarding storage of the investigational drug, agent, or biologic should be included in the protocol.

7. Requirements for Research Use of Marketed Drugs and Biologics

- 7.1. The clinical investigation of a lawfully marketed drug or biologic does not require submission of an IND if all six of the following conditions are met for exemption 1 [21 CFR 312.2(b)]:
- 7.1.1. The study is not intended to support a new indication for use or other labeling change for the product;
 - 7.1.2. The study is not intended to support a significant change in the advertising of the product;
 - 7.1.3. The study does not involve changes to a route of administration, dosage level, or use in a subject population that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the product;
 - 7.1.4. The study is conducted in compliance with requirements for IRB review [21 CFR 56] and informed consent [21 CFR 50];

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- 7.1.5. It is conducted in compliance with the requirements concerning the promotion and sale of the drugs [21 CFR 312.7]; and,
- 7.1.6. It does not intend to request exception from informed consent requirements for emergency use [21 CFR 50.24].

7.2. The clinical investigation of an *in vitro* diagnostic biological product, including blood grouping serum, reagent red blood cells, and anti-human globulin, does not require submission of an IND if the following conditions are met [21 CFR 312.2(b)(2)]:

- 7.2.1. The product is to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and,
- 7.2.2. The product is shipped in compliance with 21 CFR 312.60.

7.3. The clinical investigation involving use of a placebo is exempt from IND requirements under 21 CFR 312.2(b)(5), if the investigation does not otherwise require submission of an IND.

8. Requirements Regarding Expanded Access of Investigational Drugs

The following mechanisms expand access to investigational agents without compromising the protection of human subjects or the thoroughness and scientific integrity of product development and marketing approval ([FDA Expanded Access to Investigational Drugs for Treatment Use - Questions and Answers](#)).

The expanded access uses described in sections 8.1 – 8.5 below must meet the following criteria in order to be considered for use according to federal regulations 21 CFR 312.305(a):

- i. The patient or patients to be treated have a serious or immediately life-threatening disease or condition (e.g., advanced cases of AIDS, advanced congestive heart failure, advanced MS), and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- ii. The potential patient benefit justifies the potential risks of the treatment use, and the potential risks are not unreasonable in the context of the disease or condition being treated; and
- iii. Providing the treatment for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use, or otherwise compromise the potential development of the expanded access use.

8.1. Emergency Use IND

- 8.1.1. The FDA may authorize shipment of drug when a need for use of an investigational drug for an individual patient does not allow time for submission of an IND and the requirements of 8i – 8iii above apply, as well as the federal regulations [21 CFR

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312.310] as described in *Policy 607 Emergency Use of Investigational Drugs, Biologics, and Medical Devices*.

- 8.1.2. Prospective IRB review is required for emergency use, unless conditions for exemption from prior RSRB review and approval are met (see *Policy 607 Emergency Use of Investigational Drugs, Biologics, and Medical Devices*).

8.2. Treatment IND or Treatment Protocol

- 8.2.1. The FDA may permit use of an investigational drug under a treatment IND for a group of patients not in the clinical trial if the following requirements are met [21 CFR 312.320]:
- 8.2.1.1. The criteria listed under 8i – 8iii apply;
 - 8.2.1.2. The drug is under investigation in a controlled clinical trial under an IND in effect for the trial (for which the patient is ineligible), or all clinical trials have been completed;
 - 8.2.1.3. The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence; and
 - 8.2.1.4. There is sufficient clinical data collected to verify the drug’s effectiveness and to show there are no unreasonable risks, or the available scientific evidence, taken as a whole, concludes that the use would not expose patients to an unreasonable and significant risk of illness or injury.
- 8.2.2. Treatment IND studies require prospective RSRB review and informed consent (refer to the RSRB *Treatment Use Protocol Template* and *Treatment Use Consent Template*).
- 8.2.2.1. A physician may request a waiver from convened board review on the Form FDA 3926 for a single-patient expanded access IND. If the FDA concludes that such a waiver is appropriate, the physician must obtain concurrence from the RSRB Chair or another experienced IRB member through expedited review before the treatment begins. If the Form FDA 1571 is used for the single-patient expanded access FDA submission, a separate waiver from convened board review request can be submitted with the application.
- 8.2.3. Human gene transfer conducted under an FDA regulated individual patient expanded access IND, including for emergency use, is not research subject to the NIH Guidelines and thus does not need to be submitted to an IBC for review and approval, consistent with *Policy 608 Research Involving Genetic Testing and Gene Transfer*.

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8.3. Intermediate Patient Population IND

8.3.1. The FDA may be permit use of an investigational drug in a patient population smaller than that of a treatment IND or treatment protocol when there have been a significant number of requests made to the FDA for individual patient expanded access to an investigational drug for the same use if the following criteria are met [21 CFR 312.315]:

- 8.3.1.1. The criteria listed under 8i – 8iii above apply;
- 8.3.1.2. There is sufficient evidence that the drug is safe at the dose and duration proposed for the expanded access to justify a clinical trial of the drug in the patient population expected to receive the drug under expanded access; and
- 8.3.1.3. There is preliminary clinical evidence to support effectiveness of the drug, or a plausible pharmacologic effect of the drug to make the expanded use a reasonable therapeutic option in the anticipated patient population.

8.4. Open Label IND

8.4.1. When conducting a study to obtain additional safety data to continue treatment while an investigational drug is undergoing the process of marketing approval, prospective RSRB review and informed consent is required.

8.5. Group C Treatment IND

8.5.1. Administration of investigational drugs used under the Group C program is generally not done with research intent, as such RSRB review requirements may be waived by the FDA [21 CFR 56.105].

- 8.5.1.1. The RSRB has the authority to require review of the Group C protocol, if deemed necessary by the RSRB.

8.5.2. Informed consent is required whether or not RSRB review of the protocol has been conducted.

9. Requirements Regarding Off-Label Use of Marketed Drugs and Biologics

9.1. Physicians using a marketed product for an indication not in the approved labeling, when the intent is the practice of medicine does not require submission of an IND or review by the RSRB.

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Appendices:

None

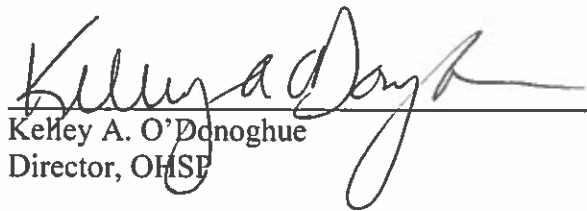
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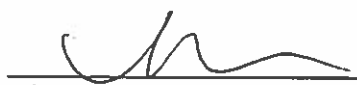
03/17/2017

Approved By:



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12/5/2019
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 Nicole Mason
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12/5/2019
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