Florida State University Human Subjects Committee

Standard Operational Procedure (SOP) 7-IRB-45

Title:	Procedures for Investigational Products
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1 INTRODUCTION

The purpose of this SOP is to determine when applications should be referred to the FDA for input and/or guidance, and outline the general responsibilities of investigators and investigator-sponsors holding an Investigational New Drug (IND) number. FDA regulations (21 CFR 56.102(c)) apply to any research experiment involving a test article in a clinical investigation involving human subjects. Use of an investigational product that is determined by the FDA to be a drug must be conducted according to FDA regulations as noted in 21 CFR Part 312, as well as other applicable FDA regulations.

The following procedures describe the review of FDA-regulated research involving any investigational product that falls under the auspices of the University. Note that this can refer to any drug (both FDA-approved or investigational), biologic or dietary supplement that, when viewed in the context of the research project, crosses over into the definition of a drug.

1.1 Definitions

1.1.1 Sponsor

The person, company, organization, or other entity that initiates and takes responsibility for a clinical investigation using an FDA-regulated item. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. The item is administered, dispensed, or used under the immediate direction of another individual.

The sponsor is almost always the holder of an IND when the research involves an item that the FDA considers investigational.

1.1.2 Sponsor-investigator

An individual who both initiates and actually conducts, alone or with others, a clinical investigation, under whose immediate direction the test item is administered, dispensed or used.

This term does not include any entity other than an individual. A sponsor-investigator has the responsibilities of both a sponsor and an investigator.

1.1.3 Drug

A drug is defined by the FDA as:

- A substance recognized by an official pharmacopoeia or formulary, or
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, or
- A substance (other than food) intended to affect the structure or any function of the body, or
- A substance intended for use as a component of a medicine but not a device or a component, part, or accessory of a device

Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process).

1.1.4 Investigational

This term is used to refer to an item that is not FDA-approved for marketing in the United States, or to an item that is being evaluated for a new and not-yet-approved indication, dosage, or formulation.

1.1.5 IND

Investigational New Drug. An IND application is the document submitted to the FDA for permission to conduct a clinical study using a drug or biologic that is new or not approved for a given dosage, formulation, or indication. When the FDA approves an IND application, it assigns an IND number to the specific use of the item.

1.1.6 Investigator's Brochure

A comprehensive document summarizing the body of information about an investigational product. The purpose of it is to compile data relevant to studies of the investigational item in human subjects, gathered during preclinical and clinical trials. It contains a "Summary of Data and Guidance for the Investigator" section, of which the overall aim is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. The sponsor is responsible for keeping the information up-to-date.

1.1.7 Botanical

A finished, labeled product that contains vegetable matter, which may include plant materials, algae, macroscopic fungi, or combinations of these. Depending in part on its intended use, a botanical product may be a food, drug, medical device, or cosmetic.

1.1.8 Supplement (dietary supplement)

A product (other than tobacco) that is:

- Intended to supplement the diet, and that bears or contains one or more of the following dietary ingredients: (a) a vitamin; (b) a mineral; (c) an herb or other botanical; (d) an amino acid; (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (f) a concentrate, metabolite, constituent, extract, or combination of these ingredients. Note that dietary supplements should not be tested/researched for any of the effects listed as defining properties of a drug as listed in Section **1.1.3**
- Not represented for use as a conventional food or a sole item of a meal of the diet, an
- Is labeled as a dietary supplement

1.1.9 Phases of Clinical Trials

Clinical trials involving new drugs are commonly classified into phases. Each phase has a different purpose.

- Phase 0: Pharmacodynamics and Pharmacokinetics. These are "first-in-human" trials. Typically, single sub-therapeutic doses of the drug are given to a small number of individuals (10-15) to gather preliminary data about pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drug).
- Phase 1: Screening for safety. The drug is tested in a small group of people (20-80) to evaluate its safety, determine a safe dosage range, and identify side effects.
- Phase 2: Establishing efficacy. The drug is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety. It may be compared against a placebo or against an approved drug designed to treat the same condition.
- Phase 3: Final confirmation of safety and efficacy. The drug is given to large groups of people (1000-3000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.
- Phase 4: Sentry studies during sales. These post-marketing studies gather additional information, including the drug's risks, benefits, and optimal use.

1.1.10 Protocol

A complete written description of a research activity involving human subjects. The protocol includes the scientific rationale as well as other information.

2 PROCEDURES

2.1 Human Subjects Office Pre-Review

The Human Subjects Office staff will conduct a pre-review of the application materials provided by the researcher to determine the level of IRB review and verify application materials (including human subjects training and Good Clinical Practice/GCP training) required for review are present in the application.

2.2 Exemptions from IRB requirement

The first step is to determine if the study is exempt from the IRB requirement. This will be part of the Human Subjects Office staff review; if there is doubt about whether a submitted study

qualifies for exemption, the IRB Chair will be consulted to assist with the determination. Criteria for exemption (per 21 CFR 56.104) include:

- Any investigation which commenced before July 27, 1981 and was subject to requirement for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.
- Any investigation which commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under FDA regulations before that date.
- Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.
- Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture. See the GUIDANCE: Exempt Research for details.

2.2.1.1 Other considerations

If the application does not involve a researcher from FSU who is engaged in the research project, then FDA regulations do not apply to the project.

If none of the above criteria apply to the project, the application is assigned to be reviewed by the IRB.

2.3 IRB Process

The FDA requires sponsors (or sponsor-investigators) to determine whether an IND is needed for a study. If the sponsor (or sponsor-investigator) thinks they might need an IND, it is strongly encouraged to contact the FDA before or at the same time as submitting to the IRB in order to avoid delays in study approval.

As part of the review process, the FDA requires the sponsor (or sponsor-investigator) to provide the IRB with its risk assessment and rationale.

If the IRB believes that the study requires an IND but the sponsor (or sponsor-investigator) does not, the IRB has the authority to require the sponsor (or sponsor-investigator) to provide or obtain confirmation from the FDA that an IND is not required (exemption determination).

The Principal Investigator is responsible to provide a plan to be evaluated by the IRB that includes storage, security and dispensing of the investigational product, and will be responsible for accounting, return, disposition, and records of accountability per the study protocol. If the IRB determines that it does not have the necessary expertise to evaluate the plan, outside consultation may be used as per SOP **7-IRB-17**.

Note that this SOP does not address emergency or compassionate use.

2.3.1 Possible IND Exemptions

2.3.1.1 For clinical investigations involving an FDA-approved drug, an IND is not necessary if all of the following conditions are met:

- The research is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug
- The research is not intended to support a significant change in the advertising for the product
- The research does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
- The research is conducted in compliance with the requirements for IRB review and informed consent (21 CFR parts 56 and 50, respectively)
- The research is conducted in compliance with the requirements concerning the promotion and sale of drugs (21 CFR 312.7)
- The research does not intend to invoke 21 CFR 50.24 (Exception from informed consent requirements for emergency research)

2.3.1.2 For clinical investigations involving an in vitro diagnostic biological product, an IND is not necessary if:

- It involves one or more of the following: (a) Blood grouping serum, (b) Reagent red blood cells or (c) Anti-human globulin
- It is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure
- It is shipped in compliance with 21 CFR 312.160

2.3.1.3 For bioavailability or bioequivalence studies of drugs not lawfully marketed in the US, an IND is not necessary if all of the following conditions are met:

- The drug product does not contain a new chemical entity, is not radioactively labeled, and is not cytotoxic
- The dose (single dose or total daily dose) does not exceed the dose specified in the labeling of the approved version of the drug product
- The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50)
- The sponsor meets the requirements for retention of test article samples (21 CFR 320.31(d)(1)) and safety reporting (21 CFR 320.31(d)(3))

2.4 Responsibilities: Record Keeping, Monitoring and Reporting Requirements

2.4.1 Principal Investigators ("Clinical Investigators in FDA regulation")

2.4.1.1 General

- Under FDA regulations and guidance, clinical investigators must be qualified by training and experience. They are responsible for the conduct of the study and for leading the team of individuals conducting the study. Before beginning participation in a clinical investigation, the clinical investigator must commit to the sponsor that he/she will follow federal regulations governing investigational drugs (including biologics).

- Ensuring the informed consent is obtained from subjects in accordance with IRB approval

- Retaining records for two years following the date the marketing application is approved by FDA or withdrawn and making those records available for inspection

- Furnishing the required reports to the sponsor, including reports of adverse events and study completion

- Providing timely reports to the IRB, including reports of changes in the research activity needed to avoid immediate hazards to participants, protocol deviations, unanticipated problems involving risks to participants or others

- Inform any potential participants that the test article(s) (i.e., drugs) are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IRB review and approval are met

- Ensuring that changes are not implemented without prospective IRB approval, unless required to eliminate immediate hazard to participants

- Complying with the requirements of the Controlled Substances Act if applicable

- Complying with all FDA test article requirements

- Adequately maintaining control of test articles, including appropriate tracking documentation for test articles to the extent that such control and documentation are not centrally administered

- Supervising the use and disposition of the test article

- Disclosing relevant financial information and conflicts of interest

- Ensuring that all associates, colleagues, and employees assisting in the conduct of the investigation(s) are informed about their obligations in meeting the above commitments

The PI/clinical investigator is additionally responsible for all requirements in the regulations as applicable to the type of research conducted.

2.4.1.2 Drug/Biologic Research—specific requirements for Principal Investigators/Clinical Investigators

- The clinical investigator must comply with the requirements specified in FDA Form 1572:
    - Personally conduct or supervise the described investigation(s)
    - Conduct the studies in accordance with the current IRB-approved protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of participants
    - Comply with all requirements regarding the obligations of clinical investigators and all other pertinent regulatory requirements
    - Immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol. §312.64; (b)
    - Read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug
    - Ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments
    - Ensure that an investigation is conducted according to the signed statement (Form FDA 1572), the investigational plan, and applicable regulations
    - Protecting the rights, safety, and welfare of participants under the clinical investigator’s care

- The clinical investigator proposing drug/biologic research will be required to ensure that investigational drugs are stored in a secure and safe manner and that the storage and safety requirements are consistent with FDA, sponsor and potential affiliated research institutions’ storage requirements for drugs being investigated. The clinical investigator is responsible for accounting, return, disposition, and records of accountability per the study protocol.

- The clinical investigator will administer the drug only to participants under the clinical investigator’s personal supervision or under the supervision of a sub-investigator responsible to the clinical investigator

- The clinical investigator will not supply the investigational drug to any person not authorized to receive it

- The clinical investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by participants.

- If the investigation is terminated, suspended, discontinued, or completed, the clinical investigator must return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug if authorized by the sponsor.

- A clinical investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data (e.g., signed and dated consent forms and medical records including, for example, progress notes and/or nurse's notes). The case history for each individual should document that informed consent was obtained prior to participation in the study.

- Clinical investigator must retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. [21 CFR §312.62]

The clinical investigator must maintain the following in their study files:

- Current curriculum vitae (CV) and human subjects/GCP training documentation

- Protocol

- Records of receipt and disposition of drugs

- List of any co-investigators with their curriculum vitae and documentation of human subjects/GCP training documentation

- Certification that all physicians, dentists, and/or nurses responsible in the study have appropriate valid licenses for the duration of the investigation

- Case histories with particular documentation on evidence of drug effects. Emphasis is on toxicity and possible untoward happenings. All unanticipated problems involving risk to subjects or others are reportable.

- IRB letters of approval

- Other documents as outlined in these Standard Operating Procedures

2.4.1.3 Additional Responsibilities When the Clinical Investigator is also the Sponsor of the IND or IDE ("Sponsor-Investigator")

These studies in question are typically investigator-initiated studies that use an investigational drug or use an approved drug for investigational purposes.

A sponsor-investigator for an IND protocol must follow the FDA regulations in 21 CFR 312 applicable to sponsor responsibilities, particularly Subpart D. This includes:

- The record keeping requirements of 21 CFR 312.57
- Promptly reporting as required in 21 CFR 312.55(b) to the FDA and all participating investigators of significant new adverse effects or risks with respect to the drug or biologic
- Selecting qualified investigators
- Providing investigators with the information they need to conduct the investigation properly
- Ensuring proper monitoring of the investigation and document monitoring activities
- Ensuring that the FDA and any reviewing IRBs or all participating investigators are promptly informed of significant new information about an investigation
- Reporting requirements to the FDA
- Sponsor-investigators who submit protocols to SBU's IRBs involving FDA test articles must include supporting FDA documentation for their IND or IDE
- The clinical investigator must submit documentation that the product preparation and manufacture meets the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND . This documentation will be subject to review by appropriate FSU entities, as determined by the Human Subjects Office staff.
- The IND or IDE product must be stored, secured, dispensed, and documented as indicated in the submission materials to the IRB, and in accordance with the requirements referenced in the preceding sections.

2.4.1.3.1 Special Considerations and requirements

The University has accountability obligations for all sponsor-investigator drug or biologic research occurring at the University. To promote compliance with FDA IND regulations the following documents must be submitted with the IRB protocol through the electronic management system**:**

- FDA Form 1571 – Investigational New Drug Application
- FDA Form 1572 – Statement of Investigator
- FDA Form 3674 – Certificate of Compliance
- IND Annual renewal report
- Copy of SAE report within 3 days of submission to FDA

JUSTIFICATION FOR THIS SOP

21 CFR 312 (Investigational New Drug Application)
21 CFR 820 (Quality System Regulation)
21 CFR 50 (Protection of Human Subjects)
21 CFR 56 (FDA General Provisions)
45 CFR 46 (Common Rule-Protection of Human Subjects)
21 CFR 54 (Financial Disclosure by Clinical Investigators)
21 CFR 11 (Electronic Records & Electronic Signature)
21 CFR 210 (Current Good Manufacturing Practice In Manufacturing, Processing, Packing, Or Holding of Drugs; General)
21 CFR 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals)
21 CFR 314 (Drugs for Human Use)
21 CFR 320 (Bioavailability and Bioequivalence Requirements)
21 CFR 330 (Over-The-Counter (OTC) Human Drugs Which are Generally Recognized as Safe and Effective and Not Misbranded) Drugs and Biologics:
21 CFR 601 (Biologics Licensing)