WAYNE STATE UNIVERSITY

HIC Policy/Procedure

Wayne State University Human Investigation Committee	
Subject	Investigational Drug Research
Form Date	January 20, 2009(Rev. 03/07/11)
Approvals	Administrative Approval 05/11/2007; Steering Committee 04/18/2007; Office of the General Counsel 01/17/2008; Administrative Approval 01/17/2009, Administrative Approval 9/30/10, Administrative Approval 03/07/11.

Background

Faculty and physicians at Wayne State University (WSU) and their affiliates may be involved in doing research on investigational drugs in one of two situations: 1) A multi-center clinical trial where the sponsor and medical director for the study have secured Food and Drug Administration (FDA) approval for such research; or 2) a local principal investigator has initiated such research and applied and received both FDA approval and licensure for conducting the research at WSU. In both cases, WSU Institutional Review Board (IRB) review and approval of the protocol must occur before the research begins.

Scope

This policy and procedure applies to all research at Wayne State University and its affiliate institutions that involves the use of a non-approved, non-marketed investigational drug or investigational use of an approved marketed product in a clinical protocol. Please see the following related HIC Policies and Procedures: “Planned Emergency Research”, “Emergency Single Time Use”, “Physician Use for Off-Label Purposes” and “Investigator-Initiated Research”, “Principal Investigator: Roles and Responsibilities”.

Definitions

Clinical Investigation – Any experiment that involves a test article (in this case – drug or biological drug) and one or more human subjects (participants) and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding non-clinical laboratory studies.

The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part [21 CFR 56.102(c)].

Investigational Drug – 1) A drug that is in clinical evaluation, for which a sponsor or PI has filed an Investigational new Drug (IND) Application with the FDA, has not been released by the FDA for general use, and is not available through regular channels of interstate commerce, but has been granted approval to use for research or humanitarian purposes by the FDA; 2) FDA approved drugs which are used in a non-FDA approved manner under a study protocol (i.e., change in therapeutic indication, dosage, route of administration); and 3) any drug that is deemed "investigational" by the FDA. For all John D. Dingell Veterans Administration Medical Center (JDD VAMC) research, any approved drug that is being studied in a controlled, randomized, or blinded clinical trial is also considered an "investigational drug" VHA Handbook 1200.5 14(b) & JDD VAMC Appendix A – Procedures for Utilizing Investigational Drugs-1.1(1), (2).

Investigational New Drug – A new drug or biological drug that is used in a clinical investigation. The term also includes a biological agent that is used in vitro for diagnostic purposes. The term investigational drug and investigational new drug are deemed to be synonymous for purposes of this part [see 21 CFR 312.3(b)].

IND – an investigational new drug application. The term IND is synonymous with "Notice of Claimed Investigational Exemption for a New Drug" [see 21 CFR 312(b)].

Investigational Pharmacist – Pharmacist at a study site or institution where the research involving the investigational drug is being conducted. The Investigational Pharmacist will ultimately dispense the study drug pursuant to authorized orders.

Phases for an IND – An IND may be submitted for one or more phases of investigation. The clinical investigation of a previously untested drug is generally divided into three phases. Although in general, the phases are conducted sequentially, they may overlap.

- Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer participants (subjects). These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects (participants) and patients included in Phase 1 studies varies with the drug, but is generally in the range of 20-80 [21 CFR 312.21(a)(1)].

  Phase 1 studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes [21 CFR 312.21(a)(2)]. Noted as "Clinical Pharmacology Trail" according to JDD VAMC Appendix A, 1.g.(1) A-1.

- Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects (participants).

- Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects (participants)[21 CFR 312.21(c)]. Noted as "Extensive Clinical Trial" according to JDD VAMC Appendix A, 1g. (3) A-2.

Treatment Use of an Investigational Drug or Biologic – Use of an investigational drug or biologic with a person or group of persons with a serious or debilitating condition where there are no other treatment options available.

IND Determination

The following is regulatory language for investigational new drugs.

According to 21 CFR 312.20(a) "A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 21 CFR 312.2(a)."

Based on federal regulations found at 21 CFR 312.2, the IND regulations apply in the following way:

(a) "Applicability. Except as provided in this section, this part applies to all clinical investigation of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)" (21 CFR 312.2a).

However, the following are exemptions to the requirements for an IND as found in 21 CFR 312.2:

(b) Exemptions.
    a. "(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:"
        i. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug,"
        ii. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product,"
        iii. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product,"
        iv. The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
        v. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
    b. (2)

i. A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with 21 CFR 312.160.
ii. In accordance with paragraph (b)(2)(i) of this section the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin."

"(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with 21 CFR 312.160."
"(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section."
"(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND."
"(6) A clinical investigation involving an exception from informed consent under 21 CFR 50.24 of this chapter is not exempt from the requirements of this part."

c. Bioavailability Studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of 21 CFR 320.31."
d. Unlabeled Indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product."

HIC Policy

Obtaining an IND

If an IND number and date is not provided on the Medical/Behavioral Protocol Summary Form submission to the HIC, and the study involves the use of an investigational drug (see Definitions), the PI will be contacted to clarify if an application for an IND has been submitted to the FDA.

If the PI does not intend to submit an IND, a written explanation of why an IND is not required must be submitted to the IRB. This explanation should include the criteria for exemption and why the project meets the criteria. A letter from the FDA should accompany this explanation.

If the FDA has determined that an IND is not required, then documentation will be required and the FDA's determination will be documented in the HIC protocol file. If an IND is required, IRB approval will not be granted until an IND number and the date that it was obtained is provided to the IRB Committee.

According to the VHA Handbook, "…an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or on earlier notification by FDA that the clinical investigation may begin."

In general, an IND need not be requested for research studies that involve the use of neutraceuticals (vitamins and other nutritional supplements) unless otherwise required by FDA. However, the PI must include information on the safety of the proposed use and dosages in the protocol that is submitted.

HIC Review and Approval of Investigational Drug Studies

All investigational drug studies must be reviewed and approved by the WSU IRB prior to starting the research. Research that requires an IND will be reviewed as follows:

- A project that meets the criteria for Expedited Review will be evaluated by the HIC Chair or his/her designee. This individual will confirm that the IND number and information provided by the researcher is valid.
- A project that meets the criteria for Full Board Review will be reviewed by the IRB Chair of the committee that will be reviewing the proposal. The IRB Chair will then assign a primary and secondary reviewer, based on scientific expertise (e.g., M.D., D.O., Pharm.D. or other clinically relevant credentials). The primary and secondary reviewer will each receive the required documentation and are responsible for verification of the IND number provided by the researcher. (Note: Researchers are instructed to submit a copy of the IND approval letter with their application.) See Medical/Behavioral Protocol Summary Form, Appendix F, "Use of Drugs, Biologic Agents, or Devices.")
- Should further input be required, a consultant with the appropriate expertise and experience with the pharmaceuticals associated with the IND will be requested to further review the submission and (1) provide written comments, or (2) attend the IRB meeting and give an oral report of his/her findings.

IRB review will include the following:

- For all VAMC research involving investigational drugs, the protocol must be reviewed by the Clinical Investigation Committee (CIC) at the JDD VAMC prior to submission to the IRB.
- Receipt and confirmation of a valid IND# with date and letter from the FDA or a letter from the FDA stating that an IND# is not required [21 CFR 312.2(b)].
- Receipt and review of the Drug Brochure and, if applicable, the Package Insert.
- Review of a detailed plan for monitoring the data and safety of all participants enrolled in the study (see HIC Policy: "Data and Safety Monitoring in Research").

Once approved, the PI must provide a copy of the approval notice to the investigational pharmacist, if the study drug is to be dispensed form there. All studies involving investigational drugs at VAMC are dispensed by the VAMC pharmacist. If requested, a copy of the approval memo may be sent directly to the VA investigational pharmacy from the IRB.

Consent

The PI is responsible to ensure that the participant has undergone a complete and informative consent process including all of the known risks, prior to beginning administration of an investigational drug.

The investigational pharmacist should be provided a copy of a signed informed consent document or verification of informed consent from the research personnel prior to dispensing any investigational drug.

The administration of an investigational drug by any route is to be delayed until adequate information regarding the actions, usage, dosage, precautions, and toxicity is available for the Pharmacy and appropriate services.

Pharmacy

All investigational drugs or biologics required by study design and supplied by the sponsor must be stored under lock and key in the investigational pharmacy or other specified location and dispensed and administered in accordance with the procedures specified below (see "Dispensing"). When the design of a study requires that drugs be dispensed from clinics or a physician's office, a specific plan for protecting the integrity of the study drug must be submitted with the protocol to the Clinical Investigation Committee (CIC) at the VAMC and the WSU IRB.

Drug Protocol

A copy of the drug protocol, pertinent information about the drug, and copies of all correspondence with the FDA, local investigator, the VA CIC, and the IRB approvals must be kept and maintained in the investigational pharmacy and the research office of the PI.

Personnel

Only the principal investigator or co-investigators listed as key personnel on the research protocol may prescribe investigational drugs. Additional information concerning the responsibilities for PIs in investigational drug studies can be found in HIC Policy/Procedures: "Principal Investigator: Roles and Responsibilities" and "Investigator-Initiated Research".

Only appropriately credentialed professionals may administer investigational drugs provided they are adequately trained and the drug information is available to them. Training records should be maintained in the study binder in the research office.

Other

The use of investigational drugs must be carried out in a responsible manner. The storage and securing procedures for drugs used in research must follow all federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations and individual institutional policies and procedures.

Fees for Investigational Drugs

Charging fees for an investigational drug in a clinical trial under an IND is not permitted without prior written approval from the FDA. Payments for an investigational study drug are negotiated in the contract between the sponsor, PI, and WSU. In requesting approval to charge a fee for an investigational drug, the sponsor must explain why the charge is necessary. In addition to obtaining FDA approval, written IRB approval to charge a fee for an investigational drug must also be secured. Information about whether or not the participant will be charged for the investigational drug must be included in the consent form. For VA studies, patients will not be charged for investigational drugs.

Procedures

Procurement

When investigational drug shipments are received at WSU or its affiliate institutions (Detroit Medical Center (DMC) or the VAMC), receipt of these must be documented in the appropriate protocol file and a drug accountability record established for each drug received. The investigational drug is delivered to the Investigational Pharmacist or designee at the VAMC and/or the DMC.

Approvals

The Principal Investigator must submit a Medical/Behavioral Protocol Summary Form submission to the IRB for all investigational drug studies with all necessary appendices, informed consent documents, investigator's drug brochure, a full protocol, and an IND number and the date that the IND was generated (if required) from the FDA. If the IND number and date is not provided, the protocol will not be approved. However, if this is the only condition placed on the protocol, it may be given specific minor revisions required by the IRB and the Chair may give full approval once the IND, date, and/or letter from FDA is provided to the IRB.

IRB approval of the investigational drug protocol must be provided to the investigational pharmacy (VAMC) or Investigational Drug Services (IDS) designee along with copy of the full protocol, informed consent document, and other information provided by the sponsor.

Prescribing

Prior to prescribing an investigational drug, the PI must ensure that full informed consent was obtained and the process fully documented in the research or medical record (in Computerized Patient Record System for VA studies). Adequate time must be taken to guarantee full patient understanding of the administration of the drug, any risks, the existence of alternative therapies, and potential effects on the health of the participant.

If the participant is unable to give consent because he/she is unconscious or has been judged incompetent by a court, has a psychiatric disorder, is incapable of comprehending the significance of such action or of exercising appropriate judgment, the consent of the patient's guardian or next of kin will be obtained (see HIC Policy/Procedure: "Obtaining Permission from Legally Authorized Representative or Family Members"). A copy of this informed consent form must be forwarded to the Investigational Pharmacy at the VAMC. For other DMC sites, an informed consent verification system may be used in lieu of the investigational pharmacy receiving a copy of each informed consent, if appropriate.

The order for the drug is sent electronically or via written prescription by the PI or designee to the investigational pharmacy.

The PI should provide the investigational pharmacist or designee with a list of names, signatures, page numbers, and phone numbers of those who have been approved to prescribe the investigational drug.

Dispensing

Investigational Drugs will only be dispensed by the investigational pharmacist when a written order authorized by the PI or designated co-investigator has been received in the investigational pharmacy.

The prescription must contain the name of the research participant, medical record/social security number, date, number and quantities of the prescribed drug, and complete directions for use.

The prescription will be labeled in accordance to state and federal regulations. The label must indicate that the drug is intended for "INVESTIGATIONAL USE".

The investigational pharmacist will not dispense the investigational drug until all required documents are received from the PI.

The PI should provide the investigational pharmacist or designee with a list of names, signatures, page numbers, and phone numbers of those who have been approved to administer the investigational drug.

The person administering the investigational drug must verify that the research participant has signed an informed consent document prior to dispensing the investigational drug.

Administration

The person(s) that have been designated to administer the investigational drug must be trained prior to giving the investigational drug, by the PI or sponsor in processes and procedures appropriate to the specific protocol. All questions should be directed to the PI, co-investigator, pharmacist, or sponsor.

Storage

All investigational drugs must be stored according to institutional policy. At the VAMC, the Chief, Pharmacy Section will designate a separate storage area for investigational drugs in the pharmacy apart from the regular drugs stored and under conditions specified by the manufacturer and secured. At the DMC, the investigational drugs are either kept in the secured investigational pharmacy or a separate section of the hospital pharmacy. On occasion, and in non-VA studies, the investigational drug may be kept under lock and key in the PI's office, utilizing secure storage conditions specified by the manufacturer.

Drug Accountability

A complete record of each drug will be maintained by the PI or his/her designee or Research Pharmacist and shall include the following:

- Name of Drug
- Manufacturer
- Quantity received
- Quantity dispensed
- Remaining balance
- Expiration date

- Lot number
- Date of authority to use
- Patient's name or Identifiers
- Patient's number
- Authorized investigator and designated person who prescribes the drug

All entries into the drug accountability log must be initialed by the pharmacist, PI, or his/her designee.

Disposal

When the investigational drug order is discontinued, all unused study drug must be returned to the investigational pharmacy (all VAMC studies), returned to the sponsor following the sponsor's specific instructions, or destroyed according to the sponsor's directions or institutional policies. If the PI is acting as the sponsor, the drug should be disposed of according to policies of the investigational pharmacy within the institution.

Records

Drug accountability records for studies shall be returned to the PI when the study is terminated. They should be kept in the research binder for at least 2 years after the drug has become commercially available, or longer, if requested by the sponsor.

Expanded Use (Treatment Use) of Investigational Drug or Biologic

The treatment Investigational New Drug Application (IND) [21 CFR312.34 and 312.35] is a mechanism for providing eligible patients with investigational drugs for treatment of serious and life-threatening illnesses for which there is no satisfactory alternative treatment. A treatment IND may be granted after data has been collected to show that the drug may be effective and does not have unreasonable risks. Because data related to safety and side-effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

Four requirements must be met before a treatment IND can be issued: (1) the drug is intended to treat a serious or immediately life-threatening disease; (2) there is no satisfactory alternative treatment available; (3) the drug is already under investigation or trials have been completed; and (4) the trial sponsor is actively pursuing marketing approval.

When a physician wishes to use an investigational drug or biologic for treatment purposes in a non-emergent situation and the patient meets the criteria set forth in the FDA regulations for a treatment IND, a prospective research protocol must be submitted to the IRB for review and approval and an informed consent must be obtained prior to the use of those drugs or biologics.

An exception to the requirement for the prior review and approval of the IRB exists when investigational drugs or biologics are required for emergency situations to safe a patient's life. This type of situation is covered by the HIC Policy/Procedure: "Emergency Single Time Use of a Test Article".

Additional Supporting Documents

The use of a treatment IND may require the submission of documents in addition to those required by this policy. See 1) Detroit Medical Center Policies: “Investigational Drug Control”, “Investigational Drug Procedure Document”, and “Investigational Medication Management”, and 2) the John D. Dingell Veterans Administration Medical Center Policy and Procedure “Investigational Drugs” and “Appendix A: Procedures for Utilizing Investigational Drugs”.