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| **Wayne State University**  **Institutional Review Board** | |
| **Subject** | 11-01 Research and Expanded Access Involving Investigational Drugs |
| **Form Date** | January 20, 2009 (Rev. March 1, 2017) |
| **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, Administrative Approval 11/30/11; Administrative Approval 03/2015; Administrative Approval 03/01/2017; Administrative, and General Counsel approval 9/2019, IRB Committee Approval 10/2019: Revisions combine policies 11- 5: Off Label Use of Drugs /and Devices, and 11-7: Compassionate Use of Drugs and Devices. |

**Background**

The U.S. Food and Drug Administration (FDA) regulates research involving investigational drugs. All clinical investigations, proposals and/or protocols involving investigational drugs must adhere to 21 CFR 50 regarding the protection of human research participants (subjects) and their proper informed consent process, documentation and 21 CFR 56 requirements in order to be reviewed and approved by the Investigational Review Board (IRB). This review and approval must occur before the investigation begins.

An unapproved investigational drug, or biologic may only be used on human research participants in the following circumstances:

1. When the drug/biologic is under clinical investigation.
2. When the use of the investigational drug/biologic falls under expanded access (compassionate use).
3. When the use of the investigational drug/biologic is for an Emergency/Single time use. See Institutional Review Board (IRB) Policy/Procedure “Emergency/ Single Time Use of Test Article” for exceptions in certain clinical care situations.

Clinical trials using investigational drugs/biologics on human participants are performed under an Investigational New Drug (IND). These clinical trials must be approved by the FDA and by the Wayne State University (WSU) IRB prior to the onset of the study.

Investigational biologics are treated the same as investigational drugs. The term "drugs" includes therapeutic biological products.

**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 IRB Policies and Procedures: “Planned Emergency Research”, “Emergency Single Time Use”, and “Investigator-Initiated Research”, “Principal Investigator: Roles and Responsibilities”.

Note: The “off-label” use of an FDA-approved, marketed drug (i.e., a use other than the indication(s) approved by FDA) by a physician for treatment purposes does not require an IND or IRB approval.

**Related WSU IRB Policies:**

* 04-02: Initial Protocol Submission Requirements
* 04-07: Continuation/Renewal of a Protocol
* 06-01: Principal Investigator Roles and Responsibilities
* 06-02: Investigator-Initiated Research
* 11-03: Emergency Single Time Use of a Test Article (Device, Biologic, Device)
* 11-06: Planned Emergency Research
* 13-01: Unanticipated Problem and Event Reporting

1. **Definitions**

**Biologic-** Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources — human, animal, or microorganism — and may be produced by biotechnology methods and other technologies. In general, the term "drugs" includes therapeutic biological products.

**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.

*Note*: *Clinical laboratory studies are not considered to be clinical investigations*.

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)].

**Neutraceuticals (Dietary Supplement)-** A dietary supplement is a product taken by mouth that is intended to supplement the diet and that contains a dietary ingredient. The dietary ingredients in these products can include vitamins, minerals, herbs and other botanicals, amino acids, other dietary substances intended to supplement the diet, and concentrates, metabolites, constituents, extracts, or combinations of the preceding types of ingredients. [[21 U.S.C. 321(ff)](https://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapII-sec321.htm)]

**Expanded Access (Compassionate Use) of an Investigational Drug or Biologic** *–*The use of an investigational drug outside of clinical trials to diagnose, monitor, or treat patients with serious or life-threatening diseases or conditions for which there are no comparable or satisfactory therapy options available

**Investigational Drug/Investigational New Drug**.– A new drug or biologic (i.e., not approved for marketing by FDA) used in a clinical investigation, including a biological product used in vitro for diagnostic purposes.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 Application (IND)** *–*An FDA application that permits an investigational drug that would otherwise be required to have pre-market approval by FDA to be legally shipped for a clinical investigation. The term IND is synonymous with “Notice of Claimed Investigational Exemption for a New Drug” [see 21 CFR 312].

**Investigational Pharmacist** *–* Pharmacist at a study site or institution where the research involving the investigational drug is being conducted. The Investigational Pharmacist is responsible for the oversight and management of investigational drugs.

**Sponsor-Investigator-** An individual who initiates (i.e., obtains an IND or IDE) and conducts an investigation and under whose immediate direction an investigational drug or device is administered, dispensed, or used. An individual who initiates a clinical trial without the support from an industry sponsor assumes the role of principal investigator and sponsor. See [WSU IRB Policy 06-02: Investigator Initiated Research](https://research.wayne.edu/irb/docs/06-02-investigator-initiated-research-8-14-2012.doc)

**2.0 IRB Policy**

Note: Unless the conditions that permit an emergency use exemption are satisfied (See WSU IRB Policy 11-03: Emergency Single Time Use of a Test Article), IRB approval must be obtained prior to initiating treatment with the investigational drug. When the request is for single-patient Expanded Access, the review may be conducted by the IRB Chair (or designee). Otherwise, the review must be conducted by the convened IRB.

**2.1 IRB Review and Approval of Investigational Drug Studies**

All investigational drug studies for which an IND is required must be reviewed and approved by a convened IRB as described by the regulations and WSU IRB policy 04-02: Initial Protocol Submission Requirements.

The following is required for the IRB review of investigational drug studies for which an IND is required:

* Receipt and confirmation of a valid IND# with date and letter from the FDA; or receipt of a valid IND# and letter from the study sponsor stating that the sponsor has an IND from the FDA for the proposed use of the study drug; 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 IRB Policy: “Data and Safety Monitoring in Research”).

During the review, the primary and secondary reviewer will verify the IND number provided by the investigator. (Note: Researchers are instructed to submit a copy of the IND approval letter with their application.) The absence of an IND number does not warrant an IRB decision to table the protocol. A specific minor modification determination may be made. The IRB and the Chair may give full approval once the IND, date, and/or letter from FDA is provided to the IRB. 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.
* 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.

See section 5.0 of this policy for information IND exemptions.

**3.0 Investigator Responsibilities:**

The investigator holds responsibilities when conducting a clinical investigation subject to FDA regulations. Please refer to WSU IRB Policy 06-01: Principal Investigator Roles and Responsibilities and WSU IRB Policy 06-02 Investigator-Initiated Research.

**3.1 IND Documentation Requirements**

If an IND is required, IND verification (IND number and the date obtained) in the form of a letter from the FDA must be included with the IRB application. IRB Approval will be withheld pending the receipt of the IND verification.

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 of the FDA’s determination should be included in the IRB application.

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.

**3.2 Investigational Drug Control, Accountability, and Record Retention**

All investigational drugs or biologics required by study design and supplied by the sponsor must be appropriately controlled, administered, stored and disposed of within FDA requirements and research site institutional requirements. Such requirements include processes to ensure that investigational products are manufactured, handled, and stored in compliance with applicable good manufacturing practices; inventory and accountability records are maintained for investigational drug receipt, dispensing, and disposition; and investigational drugs are used only in accordance with available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information and the approved protocol. For more information about investigational drug control and management, please refer to your site/institutional policies.

The PI must provide a copy of all IRB approval memos, and all approved documents including the protocol, investigator brochure, informed consent, and any other relevant documents to the investigational pharmacist. Prior to dispensing an investigational drug, the pharmacist should verify that informed consent has been obtained.

When the design of a study requires that investigational drugs be dispensed from clinics or a physician’s office, a specific plan for the appropriate controls, administration and storage as required by the FDA and research site must be described in the IRB application.

**3.2.1 Personnel**

Only the principal investigator or co-investigators listed as key personnel on the research protocol may prescribe investigational drugs if legally authorized and within their scope of practice. Additional information concerning the responsibilities for PIs in investigational drug studies can be found in IRB Policy/Procedures: “Principal Investigator: 06-01Roles and Responsibilities” and 06-02 Investigator-Initiated Research.

Only appropriately credentialed professionals may administer investigational drugs provided they are adequately educated about the investigational drug and research protocol, and drug information is made available to them. The PI should maintain the documentation of the education in the protocol records.

**3.2.2 Records**

The investigator is responsible for maintaining adequate and accurate records in accordance with FDA regulations and to make those records available for inspection by the FDA.  These records include but are not limited to: correspondence with other investigators, the IRB, the sponsor, monitors, or the FDA; drug and device accountability records; case histories; consent forms; and documentation that consent was obtained prior to any participation in the study.

Records must be maintained for a minimum 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 as such. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

Records must be obtained for a minimum 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. The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. Other regulations, such as HIPAA, organizational policies, or contractual agreements with sponsors may necessitate retention for a longer period of time.

**3.3 Charging Participants for Investigational Products**

FDA regulations do not prohibit charging participants or their insurers for investigational products so long as those charges comply with specified criteria. FDA approval of such charges does not obviate the investigator’s and IRB’s responsibility to minimize risks to subjects (Beneficence), to ensure that the risks and burdens associated with research are equitably distributed (Justice), and to ensure that subjects are properly informed and not unduly influenced to accept an otherwise unacceptable risk or cost in order to access a benefit (Respect for Persons). Any costs to participants or insurers must be described in the IRB application and informed consent document.

1. **Expanded Access (Compassionate Use) of Investigational Drug or Biologic**

Expanded access pathways, sometimes called “compassionate use”, are designed to make investigational medical products available as early in the drug evaluation process as possible to patients without therapeutic options, because they have exhausted or are not a good candidate for approved therapies and cannot enter a clinical trial.

Expanded access refers to the use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient’s disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. Except for emergency expanded access use when there is not sufficient time to secure prospective IRB review, a physician treating a patient with an investigational drug under expanded access is responsible for obtaining IRB review and approval through the usual IRB approval procedures **before** treatment with the investigational drug may begin.

Because the investigational products have not yet been approved by FDA as safe and effective, it is important to remember that the product may not be effective, there may be unexpected serious adverse effects, and appropriate measures should be taken to ensure that this is understood by the patient or their LAR and to monitor for safety.

Under FDA’s current regulations, there are three categories of expanded access:

1. Expanded access for individual patients, including for emergency use (see emergency use policy)
2. Expanded access for intermediate-size patient populations (generally smaller than those typical of a treatment IND or treatment protocol- a treatment protocol is submitted as a protocol to an existing IND by the sponsor of the existing IND).
3. Expanded access for widespread treatment use through a treatment IND or treatment protocol (designed for use in larger patient populations)

When a drug or biologic characterized as a drug is being used in a single patient, the submission can be reviewed by an IRB chair or designee rather than a fully convened board so long as the treating physician either:

* Used FDA Form 3926 for their submission to the FDA and checked the box requesting alternative IRB review procedures; or
* Used FDA Form 1571 and included a separate (letter, memo, email) request for alternative IRB review procedures

In any of these cases, the request for IRB review and approval can be submitted using the Single Patient Expanded Access Submission Form available on our Forms and Submission Requirements webpage.   
  
Expanded Access of a drug or biologic characterized as a drug through any of the three mechanisms listed above requires IRB review by a fully convened board when:

* The drug or biologic will be used to treat more than one patient
* The treating physician/PI does not have an FDA form 3926 or FDA form 1571 available
* Expanded Access use of the drug or biologic is a part of an ongoing clinical trial

In any of these cases, a full board initial submission must be submitted.

**4.1 Expanded Access Eligibility Criteria:**

* The patient must have a serious or immediately life-threatening disease or condition; there must be no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; and they generally must be unable to participate in a clinical trial
* The treating physician must determine that the probable risk from the investigational drug is not greater than the probable risk from the disease or condition
* The trial sponsor is actively pursuing marketing approval of the drug for the expanded access use
* If the physician’s practice includes multiple patients who might be good candidates for the investigational product, consider whether an expanded access IND for an intermediate-size population, rather than multiple single patient INDs, would be more efficient.

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 save a patient’s life. This type of situation is covered by the IRB Policy/Procedure: “Emergency Single Time Use of a Test Article”.

**4.2 Submission Requirements for Expanded Access of an Investigational Drug:**

Physicians using investigational drugs under expanded access to treat more than one patient under the criteria described in section 4.1 of this policy will need to follow the submission requirements and Full Board IRB review procedure described in WSU IRB Policy 04-02: Initial Protocol Submission Requirements

**4.2.1: Expanded Access to Investigational Drugs for Individual Patients:**

Physicians using investigational drugs under expanded access to treat a single patient under the criteria described in section 4.1 of this policy should develop and submit an appropriate plan and schedule for treating and monitoring the patient, taking into consideration the nature of the investigational drug and the needs of the patient. The plan should include monitoring to detect any possible problems arising from the use of the investigational drug.

To request IRB approval for Expanded Access Single Time Use, investigators should contact the IRB office and submit the following:

1. A completed Expanded Access Application Form and any additional documentation noted within it;
2. A copy of the information submitted to the FDA (and FDA approval, if available);
3. A copy of the drug brochure, Instructions for Use, or other similar documentation that provides information regarding the potential risks and benefits of the drug;
4. A copy of the plan for treating and monitoring the patient; and
5. A copy of the draft informed consent document.

The IRB may review the expanded access application prior to FDA approval being received but may condition approval upon receipt of FDA approval. The IRB will provide the investigator with written documentation of its review.

Wayne State University will consider reliance upon an external IRB for Expanded Access protocols on a case-by-case basis when the IND is held by a commercial sponsor and an external IRB has already approved the protocol and is willing to accept review and oversight of additional investigators/sites. Investigators should contact the IRB administration office, to discuss IRB reliance for Expanded Access protocols.

**5.0 IND Exemptions**

For drugs, an IND is not necessary if the research falls in one of the following seven (7) categories:

1. [21 CFR 312.2(b)(1)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.2): The drug being used in the research is lawfully marketed in the United States and all of the following requirements are met:
   1. The research is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug;
   2. In the case of a prescription drug, the research is not intended to support a significant change in the advertising for the product;
   3. The research does not involve a route of administration, dose, 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;
   4. The research is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts [56](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56) and [50](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50), respectively];
   5. The research is conducted in compliance with the requirements of [21 CFR 312.7](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7) (i.e., the research is not intended to promote or commercialize the drug product); and
   6. The research does not intend to invoke FDA regulations for planned emergency research [[21 CFR 50.24](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24)].

Please Note: FDA has provided specific [guidance](https://www.fda.gov/downloads/Drugs/Guidances/UCM071717.pdf) for evaluating whether this exemption applies to studies of marketed drugs/biologics for the treatment of cancer.

1. [21 CFR 312.2(b)(2)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.2): For clinical investigations involving defined (blood grouping serum, reagent red blood cells, and anti-human globulin) in vitro diagnostic biological products, an IND is not necessary 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 [312.160](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.160)
2. [21 CFR 312.2(b)(5)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.2): A clinical investigation involving use of a placebo is exempt from the requirements of part 312 if the investigation does not otherwise require submission of an IND.
3. [21 CFR 320.31(b) and (d)](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.31): Bioavailability or Bioequivalence (BA/BE) studies if all of the following conditions are met:
   1. The drug product does not contain a new chemical entity [[21 CFR 314.108](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.108)], is not radioactively labeled, and is not cytotoxic;
   2. 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;
   3. The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts [56](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56) and [50](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50), respectively]; and
   4. The sponsor meets the requirements for retention of test article samples [[21 CFR 320.31(d)(1)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.31)] and safety reporting [[21 CFR 320.31(d)(3)](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=320.31)].
4. [21 CFR 361.1](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=361.1): Research using a radioactive drug or biological product if all of the following conditions are met:
   1. It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
   2. The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
   3. The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
   4. The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.
5. FDA practices [enforcement discretion](https://www.fda.gov/downloads/drugs/guidances/ucm229175.pdf) for research using cold isotopes of unapproved drugs if all of the following conditions are met:
   1. The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
   2. The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;
   3. The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
   4. The quality of the cold isotope meets relevant quality standards; and
   5. The investigation is conducted in compliance with the requirements for IRB review and informed consent. [21 CFR parts [56](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56) and [50](https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50), respectively]