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Written By:	B. Laurel Elder
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USE OF INVESTIGATIONAL DRUGS OR BIOLOGICS IN HUMAN SUBJECTS RESEARCH

A. Procedure Contents – this procedure contains information on the following topics:

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This procedure describes the regulations and WSU IRB procedures for use of investigational devices. If the devices are to be used in the hospital setting, investigators must consult the research offices at the individual institutions (e.g. MVH, GSH, VA etc.) and meet the requirements of the institution before a device can be used in a patient.

B. Background

Federal law prohibits the distribution of new drugs or biologics until the FDA has reviewed clinical data and determined that a particular product is safe and effective for a specific use in human subjects.

In order to test a new drug or biologic in clinical trials, it is necessary to obtain an exemption from this law. Thus a drug sponsor is required to apply for an Investigational New Drug (IND) exemption before tests with human subjects may begin.

In general, the review requirements for biologics are the same as those for drugs. Accordingly, unless otherwise indicated, the provisions that follow use of the term "drug," apply to biologics as well as to drugs. The investigator is responsible for obtaining the IND number and providing it to the IRB. Studies that involve FDA-regulated products that are submitted without a IND number will be reviewed by the IRB with respect to determining the need for an IND, based on federal requirements and the investigator's response to questions contained in the protocol.

If the IRB determines that the study does not require an IND and approves the study, the study may begin. If the IRB determines that an IND is needed, the investigator/sponsor must submit an IND application to the FDA and provide documentation of the outcome of the FDA determination (IND number) to the IRB before the IRB gives approval to enroll subjects in the study.

An IND is an application to the FDA for permission to test a drug to determine if it is safe and effective. The process is governed by 21CFR 312.

C. Exemption for Drug/Biologics

The IRB may consider a study using a drug product that is lawfully marketed in the United States to be exempt from the requirements for obtaining an IND if all the following apply:

- 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;
- 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;
- The investigation does not involve a route of administration or dosage level or use in a subject population (e.g., children, prisoners, pregnant women and fetuses) or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- The investigation is conducted in compliance with the requirements for institutional review and with the requirements for informed consent; and
- The investigation is conducted in compliance with the requirements with regard to promotion

D. When is an IND needed?

1. If a newly developed drug/biologic that is not approved by the FDA and not licensed for marketing in the US is to be tested for safety and efficacy in one or more human subjects.
2. If a drug/biologic previously approved by the FDA and licensed for marketing in the US is to be studied in one or more human subjects:

- with the intent to generate data leading to the approval of a new advertising claim. (For example the manufacture would like to be able to advertise that this new drug is as good as or better than an approved product.)
- for a new clinical indication (For example the drug may be approved for one clinical indication such as cognitive impairment in Alzheimer's, but there is a desire to see if those with cognitive impairment due to multiple sclerosis could also be helped.)
- in a population for which it was not previously approved.(For example if the product is approved when used in adults but there is a desire to use the product in minors.)
- if the drug/biologic is being given in an unapproved formulation, route or delivery system. (For example if the product is approved when given intravenously however there is a desire to be able give this product orally.)

3. Unapproved combinations of approved concurrent therapies require an IND. (For example if there are 2 approved chemotherapeutic agents available for a certain diagnosis and there is a desire to see if better response and lower toxicities could be experienced if the products were used concurrently.)
4. If a dietary supplement or botanical is being studied for its effect on disease in the proposed investigation (i.e., to cure, treat mitigate, prevent or diagnose disease including its associated symptoms, then it may be considered an investigational new drug and may be subject to IND requirements.

E. When is an IND not required (exempt from IND)?

An IND is not required if the drug/biologic under study is already licensed and approved by the FDA for marketing in the USA, if all of the following study conditions are met:

- The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any significant change in the labeling for the drug/biologic
- The drug/biologic that is undergoing investigation is lawfully marketed as a prescription drug/biologic product and the investigation is not intended to support a significant change in the advertising for the product.
- 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/biologic product.
- The investigation is conducted in compliance with the requirement for institutional review set forth in 21CRF 56 and with the requirements for informed consent set forth in 21CFR 50.
- The investigation is conducted in compliance with the requirements of 21CRF 312.7 - meaning that the drug/biologic may not be represented as safe or effective for the purposes for which it is under investigation nor may it be commercially distributed or test marketed or sold.

If all of these conditions are met, then the study is considered IND exempt.

F. Types of INDs.

- **Commercial IND :** The IND application is submitted by a commercial sponsor or manufacturer (like Pfizer or Merck, etc.) and serves as the first step towards the creation of the package insert and marketing of the drug.
- **Investigator-initiated IND :** The IND application is initiated by the investigator that will also be conducting the investigation and under whose immediate direction an investigational drug/biologic is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population. In this case the PI assumes the responsibilities of "sponsor" as well as PI.
- **Treatment IND :** A Treatment use IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.. A Treatment IND allows for treatment use while Phase II or III studies are underway.
- **Emergency Use IND :** allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR , Sec. 312.233 or Sec. 312.34. It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

G. Who makes the determination regarding need for IND application?

The determination of whether or not an IND application is required is made by the IRB. The FDA may over-rule the IRB regarding the need for an IND.

H. IND (and IDE) Applications

The IND or IDE application must contain sufficient data from animal and in vitro studies to demonstrate the likelihood that the product will be safe and effective for the purpose indicated. If the FDA agrees that the data are sufficient to support a decision to initiate clinical trials, and the proposed protocol is acceptable, the FDA will provide an IND or IDE number to the protocol. Specific requirements for protocol design are set forth in FDA Regulations.

IDE: The investigator is required to wait for the FDA scientists to review the materials submitted, and if necessary request additional information, require modifications, and approve or disapprove the application before proceeding with the clinical trial. The IRB will not provide approval to enroll subjects in the study until the FDA has either provided an IDE number or advised the principal investigator that an IDE is not required.

IND : The investigator is required to wait 30 days after submitting the IND application to the FDA before enrolling subjects. During this time the FDA scientists will review the materials submitted, and if necessary request additional information or require modifications. The FDA may send the sponsor an IND #, however this is not an approval to proceed. The IRB will not provide approval to enroll subjects in the study until the 30 day time period has passed.

I. IND Review Process by the FDA

Most INDs are passively approved. When the FDA receives the application, the FDA assigns an IND number. A letter is sent to the applicant providing the IND number, however, this number should not be mistaken as an "approval letter." In most cases, passive approval is assumed if there has been no formal contact from the FDA within 30 days of the submission of the IND application to the FDA. Studies cannot be initiated until after the 30-day period (and until the IRB has approved the study).

J. Maintaining an IND

When the PI has an "approved" IND, the PI is also referred to as the "holder of the IND." The PI takes on the responsibilities of sponsor as defined in the regulations. Once the 30-day waiting period is over and the study is approved by the IRB, the PI may initiate the research project.

Responsibilities of the PI as IND holder are as follows:

1. The PI is expected to update or file amendments to the IND with the FDA in a timely fashion when:
    - the protocol and/or consent is/are amended in a manner that affects the safety of subjects, the scope of the investigation, or the study design.
    - when an adverse event occurs that is considered serious, unexpected and related/possibly related, a report should be submitted to the FDA via telephone or fax within 7 days. A written report should be sent to the FDA within 7 days. Unanticipated problems must also be reported within 7 days.
    - each time a new investigational site is added (if the study is multi-site) the PI/IND holder must submit the documentation for that site including the FDA 1572 and current dated and signed CVs.
    - each time a new investigator is added. An amended FDA 1572 and current dated and signed CV will be anticipated by the FDA.
    - the anniversary date of the IND is within 60 days of the original IND submission date. An annual progress report to the FDA regarding research activity taking place under the IND should contain the following elements:
        - a completed FDA 1571 numbered sequentially
        - title(s) of the protocol(s) operating under the IND with detailed enrollment information for each protocol (# enrolled to date, # entered since last report, # in study treatment, # in follow up, #

completed, # withdrawals. Each of these numbers should be reported by totals and then by age group, gender and race.
- A summary for each protocol operating under this IND of the most frequent and most serious adverse events organized by body system for each protocol
- A summary for each protocol operating under this IND of all IND Safety reports for the last year.
- A list of all deaths noting the cause of death for each protocol operating under this IND.
- List of withdrawals noting the reason for withdrawal for each protocol operating under this IND.

Each update or amendment to the IND should contain:
- completed FDA Form 1571 numbered sequentially.
- Cover letter or narrative describing the purpose of the submission.
- Documentation for the amendment. (For example, if the protocol is being modified, then a copy of the protocol should be submitted. If a Serious Adverse Event is being reported then a FDA Form 3500A MedWatch or CIOMS (www.cioms.ch) should be submitted.)

2. The PI is expected to keep all data secure.
3. All data is expected to verifiable. This means that adequate source documentation and data collection forms are maintained. Please refer to the FDA websites for additional information.
4. A copy of all communications to the FDA must also be submitted to the WSU IRB.

K. Phases of Studies

The FDA requires various stages of human subject research to ensure that drugs and biologics are both safe and effective for the proposed use. This safety and efficacy data may eventually be used in marketing materials or on the drug's label or package insert.

Phase One Drug Trials

Phase 1 drug trials include the initial introduction of an investigational new drug into humans. These studies are typically closely monitored and conducted with healthy volunteers; sometimes, where the drug is intended for use in subjects with a particular disease, however, such subjects may participate as subjects. Phase 1 trials are designed to determine the metabolic and pharmacological actions of the drug in humans, the side effects associated with increasing doses (to establish a safe dose range), and, if possible, to gain early evidence of effectiveness; they are typically closely monitored. The ultimate goal of Phase 1 trials is to obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled sufficiently valid Phase 2 studies. Other examples of Phase 1 studies include studies of drug metabolism, structure-activity relationships, and mechanisms of actions in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease

processes. The total number of subjects involved in Phase 1 investigations is generally in the range of 20-80.

Phase Two Drug Trials
Phase 2 trials include controlled clinical studies conducted to evaluate the drug's effectiveness for a particular indication in subjects with the disease or condition under study, and to determine the common short-term side effects and risks associated with the drug. These studies are typically well-controlled, closely monitored, and conducted with relatively small numbers of subjects, usually involving no more than several hundred subjects.

Phase Three Drug Trials
Phase 3 drug trials involve the administration of a new drug to a larger number of subjects in different clinical settings to determine its safety, effectiveness, and appropriate dosage. They are performed after preliminary evidence of effectiveness has been obtained, and are intended to gather necessary additional information about effectiveness and safety for evaluating the overall benefit-risk relationship of the drug, and to provide an adequate basis for physician labeling. In Phase 3 studies, the drug is used in the way it would be administered when marketed. When these studies are completed and the sponsor believes that the drug is safe and effective under specific conditions, the sponsor applies to the FDA for approval to market the drug. Phase 3 trials usually involve several hundred to several thousand subject-subjects.

Phase Four Drug Trials
Concurrent with marketing approval, the FDA may seek agreement from the sponsor to conduct certain post-marketing (Phase 4) studies to delineate additional information about the drug's risks, benefits, and optimal use. These studies could include, but would not be limited to, studying different doses or schedules of administration than were used in Phase 2 studies, use of the drug in other subject populations or other stages of the disease, or use of the drug over a longer period of time.

Research concerning new treatments for certain life-threatening conditions (e.g., cancer, AIDS, emergency-room interventions) may progress differently through the four phases. Investigators interested in studying such products should contact the FDA for further information.

L. Permissible Exceptions for Subject Care

1. Off-Label Use

The FDA permits the "off-label" use of an approved product (for a purpose or at a dosage different from approved uses) in the course of professional practice (i.e., for the care of individual subjects). When it occurs with the intention of contributing to generalizable knowledge or the physician contemplates reporting the results - even as a collection or

series of case studies - the activity is viewed as research and thus is subject to prior IRB review and approval.

2. Compassionate Use

Compassionate Use is an FDA regulatory term ONLY for devices. Compassionate Use is not a regulatory term under regulations covering investigational drugs/biologics. On the drug side the terminology of Treatment Use is used informally for both Treatment Use and Compassionate Use. Refer to Treatment Use (below) for more information.

3. Emergency Use/Single Patient IND

Emergency Use of an Investigational Drug
FDA Requirements (Single Patient IND)
Additional Clarification

IRB Process for Emergency Use/Single Patient IND:

1. The Principal Investigator should communicate with the sponsor (drug manufacturer) and the FDA to confirm that all FDA requirements are being met for emergency use.
2. If Emergency Use is approved by the Sponsor/ FDA consent should be obtained from the patient using a consent form provided by the sponsor.
3. If the patient is unable to give consent, the physician must provide written documentation from him/her and another physician not involved in the clinical trial, verifying the following criteria:
    1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
    2. Informed consent cannot be obtained because of an inability to communicate with , or obtain legally effective consent from the subject
    3. Time is not sufficient to obtain consent from the subject's legal representative
    4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
4. The drug/ biologic may then be given to the patient.
5. The Principal Investigator must notify the IRB in writing within 5 working days stating that he/she has used the Emergency Use provision. A copy of the consent form or the documentation verifying consent could not be obtained should be attached. A form for IRB notification can be found on the WSU IRB web site.
6. Following the next IRB meeting the Principal Investigator will receive notification from the IRB verifying that the board concurred with the emergency use.

The FDA allows for only one emergency use of a test article without prospective IRB approval. See FDA Requirements above for additional information. If investigators expect

to have an additional patient(s) who will need the same test article they must submit a protocol to the IRB.

4. Treatment Use

FDA Requirements

"Treatment Use" is described in the federal regulations to facilitate broader availability of promising new therapies to desperately ill patients as early in the development process as possible. Under these regulations, patients faced with a serious or life-threatening disease/condition for which no alternative exists may receive investigational therapy outside of the controlled clinical trial.

Treatment Use may be considered when:

1. The drug/device is intended to treat or diagnosis a serious or immediately life-threatening disease or condition
2. There is no comparable or satisfactory alternative drug/device available to treat or diagnose the disease or condition in the intended patient population.
3. The drug/device is under investigation in a controlled clinical trial for the same use under an approved Investigational Device Exemption (IDE) or Investigational New Drug (IND) application, or all clinical trials have been completed; AND
4. The sponsor of the controlled clinical trial is pursuing marketing approval/clearance of the investigational drug/device with due diligence.

IRB Process for Treatment Use:

1. The Principal Investigator either through the sponsor or directly with the FDA must obtain a "Treatment Use IND/IDE"
2. The Principal Investigator will then submit a new protocol application to the IRB following procedures for a Full Board Study.

M. Record Requirements

1. **Disposition of drug.** An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under Sec. 312.5947.

2. **Case histories.** An 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 including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses` notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

3. **Record retention.** An investigator shall retain records required to be maintained under this part 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.

4. **VA requirements –** all VA investigators must consult with the VA research office, since the VA may have additional record requirements

N. IND Closure

An investigator may withdraw an IND at any time with or without cause. A letter to the FDA is required and copy should be forwarded to the IRB.

The FDA may place an IND on "Clinical Hold" for a number of reasons. Clinical hold means that all study activity is halted pending the FDA-required modifications. When a clinical hold is placed, the IND initiator usually has 30-days to respond back to the FDA.

- A Clinical Hold may be issued if it appears subjects are being exposed to greater risk than had originally been recognized. Enrollment is halted and subjects currently being treated may only continue on study drug if it is clinically necessary for them to do so. The Clinical Hold is often lifted after adjustments have been made to the study design.
- A Clinical Hold may also be issued if the researcher's qualifications are called into serious question or if the study design proves fatally flawed in such a way that no meaningful data will be gleaned and/or no meaningful results will be determined from the data.

The FDA may also terminate an IND if clear and compelling danger to the research subjects is present or if there is evidence of fraud on the part of the investigator. Termination is usually only undertaken when reactivation is not anticipated.

O. Investigators as Sponsors

If an investigator is the developer of the drug, biologic or medical device, and no commercial manufacturer is involved, then the investigator is also the sponsor for the purposes of designing and organizing clinical trials.

Sponsors also have important administrative and reporting requirements above and beyond those of investigators. Faculty contemplating the dual role of sponsor-investigator should consult with the Wright State Research Institute about the additional responsibilities that entails.

The sponsor must declare any individual financial conflict(s) of interests in the research and develop a management plan that is approved by the University.

P. Multi site trials:

Should an investigator associated with WSU sponsor a multi-site study, that investigator is required to meet all the responsibilities of a sponsor as determined by DHHS guidance.

At the time of initial review the IRB will require information on procedures for dissemination of protocol information (e.g. unanticipated problems involving risks to subjects or others, protocol modifications, interim findings) to all participating sites. In addition the WSU PI must ensure that investigators at other research sites submit and follow requirements directed by their local IRBs.

IRB policies and procedures from each approving institution will be followed by researchers at that site. All required reports will be provided to the local IRB as per their policy. The coordinating PI at WSU will be responsible for providing local information as well as unanticipated problems involving risks to subjects or others, protocol modifications, or interim findings that may affect the WSU IRB's continuing approval of the research.