# INVESTIGATIONAL NEW DRUG APPLICATION (IND) EDUCATIONAL HANDOUT

Institutional Review Board and Human Subjects Office

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## I. Introduction

The following information is provided to guide sponsor-investigators (SI) who hold an Investigational New Drug Application (IND) in understanding and complying with the federal regulations that pertain to the conduct of research with an investigational drug.

The federal regulations for INDs are found at 21 CFR 312. Hyperlinks to the IND regulations are included throughout so researchers may refer to the complete text of the corresponding regulations.

For more information about obtaining an IND and applicable forms and instructions, see 21 CFR 312 Subpart B Investigational New Drug Application and Information for Sponsor-Investigators Submitting Investigational New Drug Applications.

Sponsor-investigators are also required to follow all federal regulations and University of Iowa policies and guidance for human subjects research. University of Iowa policies and guidance for human subjects research are available on the Human Subjects Office website.

## II. Definitions

**What is an IND?**
An IND is an application submitted to the Food and Drug Administration (FDA) whereby a drug sponsor requests authorization from the FDA that will allow the interstate transport of investigational agents for administration to humans. The sponsor may be an individual, pharmaceutical company, government agency, academic institution or private organization. For additional information on the content and format of IND application, see 21 CFR 312.23.

**What is a Sponsor?**
A sponsor is an individual or other entity that takes responsibility for and initiates a clinical investigation. The sponsor does not actually conduct the investigation.

**What is an Investigator?**
An investigator is an individual who actually conducts a clinical investigation. S/he is responsible for the administration and/or dispensing of the test article. If a team of individuals conducts the research, the investigator is responsible for the conduct of the team.

**What is a Sponsor-Investigator?**
A sponsor-investigator (SI) is an individual who initiates (i.e., obtains an IND) and conducts an investigation and under whose immediate direction an investigational drug is administered, dispensed, or used.

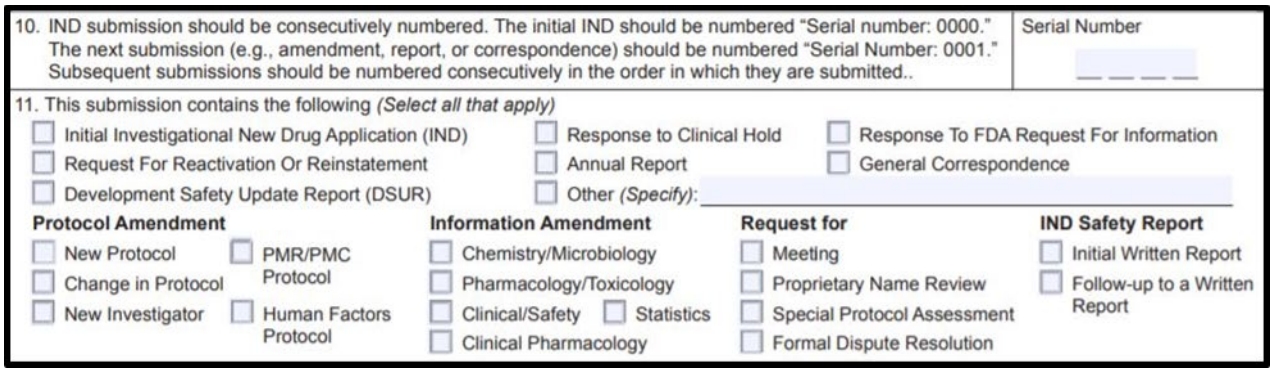
When an investigator holds an IND for the product being tested in a particular research study, s/he must also assume all the responsibilities of the sponsor, and is called a "sponsor-investigator." Therefore, the regulatory requirements of a sponsor- investigator include those applicable to an investigator and a sponsor. 21 CFR 312 Subpart D.

**What is a Clinical Hold?**
A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold may apply to one or more of the investigations covered by an IND. A complete clinical hold is a delay or suspension of all clinical work under an IND. A partial clinical hold is a delay or suspension of only a part of the clinical work under an IND.

**What is a FDA Form 1571?**
The FDA Form 1571 or '1571' is the IND application cover page and it must accompany the initial IND submission and any amendments, IND safety reports, annual reports or general correspondence the sponsor submits to the FDA about the IND. The 1571 is a contractual agreement between the sponsor and the FDA. By signing the 1571, the SI agrees to the following:

- S/he will not begin the clinical investigations until 30 days after the FDA's receipt of the IND, unless the sponsor receives earlier notification from the FDA
- S/he will not begin or continue the investigations covered by the IND if the FDA has placed the investigations on clinical hold
- S/he will conduct the investigation in accordance with all other applicable regulatory requirements
- An IRB that complies with 21 CFR 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation under the IND

**Submission to FDA:** IND submissions should be consecutively numbered. In Section 10 of the 1571, the initial IND submission should be numbered '000'; and subsequent submissions should be numbered consecutively in the order they are submitted (001, 002). For the initial IND submission, only the 'Initial Investigational New Drug Application (IND)' box should be checked in Section 11 of the 1571. Because subsequent submissions may contain more than one type of information, all boxes that correspond to the new information included in the submission should be checked. The FDA website states that the initial IND submission and each subsequent submission to the IND must be submitted to the FDA in triplicate (the original and two photocopies are acceptable); however, the requirements of individual reviewing divisions may vary. The SI should confirm the requirement with the FDA contact person assigned to the IND application review. (See Section III of this guidance).



10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..

Serial Number

11. This submission contains the following *(Select all that apply)*

- ☐ Initial Investigational New Drug Application (IND)
- ☐ Request For Reactivation Or Reinstatement
- ☐ Development Safety Update Report (DSUR)
- ☐ Response to Clinical Hold
- ☐ Annual Report
- ☐ Other *(Specify)*:
- ☐ Response To FDA Request For Information
- ☐ General Correspondence

**Protocol Amendment**

- ☐ New Protocol
- ☐ Change in Protocol
- ☐ New Investigator
- ☐ PMR/PMC Protocol
- ☐ Human Factors Protocol

**Information Amendment**

- ☐ Chemistry/Microbiology
- ☐ Pharmacology/Toxicology
- ☐ Clinical/Safety
- ☐ Statistics
- ☐ Clinical Pharmacology

**Request for**

- ☐ Meeting
- ☐ Proprietary Name Review
- ☐ Special Protocol Assessment
- ☐ Formal Dispute Resolution

**IND Safety Report**

- ☐ Initial Written Report
- ☐ Follow-up to a Written Report

**What is ClinicalTrials.gov?**

ClinicalTrials.gov is a clinical trial registry and results data bank operated by the National Library of Medicine (NLM) at the National Institutes of Health (NIH). Section 801 of the FDA Amendments Act (Food and Drug Administration (FDAAA 801) requires the registration and submission of the results of applicable clinical trials – which include those involving FDA INDs. The federal registration deadline is no later than 21 days after enrollment of the first participant, but the UI IRB generally requires registration prior to granting initial IRB approval for UI investigator initiated studies. If there is a plan to publish the data, the International Committee of Medical Journal Editors requires registration prior to the enrollment of the first subject. After submission to ClinicalTrials.gov, a review process occurs to ensure the record is completed appropriately. Once accepted, the National Clinical Trial (NCT) number will be assigned UI investigator-initiated studies must document the PI as the "Responsible Party" by listing the PI as 'Sponsor-investigator'. The NCT number must be listed in HawkIRB Section VII.B.1.b if the study meets the definition of an Applicable Clinical Trial. Contact the HSO for assistance obtaining a username with the ClinicalTrials.gov Protocol Registration and Results System.

**What is a FDA Form 3674?**

The FDA Form 3674 is a 'Certification of Compliance' to assist with meeting the requirements of Clinical Trials.gov Data Bank outlined in 42 U.S.C. § 282(j)(5)(B), section 402(j)(5)(B) of the Public Health Service (PHS) Act. This requirement went into effect on December 26, 2007. The form provides the FDA with the information required of applicants who submit certain human drug, biological product, and device applications,

including Investigational New Drug Applications (IND) and new clinical protocols submitted as an amendment to an existing IND.

**Submission to the IRB:** The IRB expects the SI to scan and attach to the IRB application the entire contents of the submission that was sent to the FDA. This includes the following documents: initial completed/signed 1571, protocol and the investigator's brochure. This must be clearly labeled and included in the 'Sponsor Documentation' category on the Attachments Page. If these are submitted as one document, the IRB may request that they are separated into individual documents and attached in the appropriate category (protocol, sponsor documentation). In addition, either documentation showing the date the FDA received the application or FDA approval to proceed is required in the Sponsor Documentation category.

At the time of subsequent IND submissions to the FDA, the SI should also notify the IRB of the submission via a modification to the IRB Application. The corresponding 1571 should be uploaded ''on top' of the previous 1571 version(s) on the IRB Attachments Page, using the 'Edit Electronic Attachment' instructions. The IRB modification should include an attachment documenting that the amendment was sent to the FDA and the date it was sent.

**What is a FDA Form 1572?**
The Form FDA 1572 or '1572' is also called the 'Statement of Investigator'. It is a legally binding contract between the investigator and the FDA, whereby the investigator agrees to provide specific information to the sponsor and assures that s/he will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug.

By signing this form, the investigator assumes full responsibility for the study, attests that s/he has read the protocol and/or Investigator's Brochure and agrees to conduct the study according to the protocol and FDA regulations.

Each investigator that conducts the clinical trial and under whose supervision the study drug is administered must complete a 1572 prior to participating in an IND study. Additionally, s/he must update any changes to the information during the course of the study.

The PI is not required to attach the 1572 to the IRB Application.

## III. FDA Receipt of an IND application

Upon receipt of the IND application, the FDA assigns an IND number and forwards the application to the appropriate reviewing division. The reviewing division will send an IND Acknowledgement notification to the SI. This provides the assigned IND number, date of receipt of the original application, the address to send future IND submissions, and the name and telephone number of the FDA person to contact with questions about the application. It informs the SI that s/he may not begin the study until 30 days after the receipt date or upon FDA notification about the status of the application. This allows the FDA time to evaluate the application and determine if it is safe to proceed.

After review, the FDA may:

- Grant the IND
- Grant an IND exemption
  - The FDA can exempt a clinical investigation of a drug product that is lawfully marketed in the United States from the requirements for an IND if it meets certain criteria [21 CFR 312.2(b)]

- Place the IND Application on a Complete or Partial Clinical Hold
  - When a proposed study has been placed on hold, the study may not begin, and investigational drug may not be administered to research subjects
  - Holds may require modifications to and resubmission of the protocol to the FDA. If approved, the modifications should be submitted to the IRB

In the event the IRB determined that an IND is required, but the FDA disagrees, the investigator must attach documentation of the FDA's determination that an IND is not required. This documentation can be an email or letter from the FDA. The SI should clearly label and upload it in the Sponsor Documentation or Miscellaneous category of the Attachments Page of the IRB application. See Information for Sponsor-Investigators.

## IV. What are the sponsor-investigator's responsibilities as a *sponsor*?

The SI assumes all responsibilities toward co-investigators that are normally assigned to the sponsor and is responsible for maintaining an effective IND with respect to the investigations. These responsibilities include:

### A. Selection and monitoring of investigators [21 CFR 312.53]

- Selecting qualified investigators based on training and experience
- Obtaining a current CV from each investigator
- Obtaining a signed Form FDA 1572 from each investigator
- Providing investigators with the information they need to conduct the investigation properly
- Ensuring the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND
- Ensuring that the study drug is shipped only to participating investigators
- Reviewing on-going investigations
- Informing co-investigators of new observations with regard to the investigational drug and progress of the study
- Selecting qualified monitors and ensuring proper monitoring of the investigation
- Assuring compliance of all investigators with the protocol
- Reviewing and evaluating safety and efficacy data of the investigational drug
- Discontinuing studies that are deemed to pose an unreasonable and significant risk to subjects
- Ensuring the FDA and all participating investigators are promptly informed of significant new adverse events (AE) or risks with respect to the drug in safety reports as described

below
- Assuring that all participating investigators return any unused supplies of the investigational drug to the SI, or otherwise provide for disposition of the unused supplies of the drug under 21 CFR 312.59, if the investigation is terminated, suspended, discontinued or completed

## B. Reporting Requirements

Once the IND is submitted and becomes effective, the SI must report the following information to the FDA.

### 1. Protocol Amendments

- **New protocol** [21 CFR 312.30(a)]
  Once the IND is in effect, the SI must submit a new protocol amendment to the FDA for any new or modified protocol not contained in the IND application.

  The modification should include the new or modified protocol as well as documentation that the protocol amendment was submitted to the FDA and the date of submission. The study may not begin until the new protocol has been submitted to the FDA for review and been approved by the IRB.

  **UI IRB policy**
  If the SI submits a new protocol to his/her IND application, the IRB expects that the IND holder maintain one IRB application that contains the entirety of the IND application and includes a full history of the initial submission and all amendments that are submitted to the FDA.

  Each ancillary study that is relevant to this IND application and to be conducted at the UI should be submitted in a separate IRB application, include the required IND information relevant to the ancillary study only and reference the IRB ID# of the main IND study in Section I.4.

  All amendments must also be submitted to, reviewed and approved by the IRB before implementation.

- **Changes in the protocol** [21 CFR 312.30(b)]
  Protocol amendments are necessary when a sponsor wants to change a previously submitted protocol or add a study procedure not submitted in the original IND.

  The following protocol changes must be submitted to the FDA.
  - For *Phase 1 studies,* any change that significantly affects the safety of subjects
  - For *Phase 2 and 3 studies*, any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study

- **New investigator** [21 CFR 312.30(c)]
  The addition of a new investigator must be reported to the FDA within 30 days of the investigator being added. Once the investigator is added to the study, the

investigational drug may be shipped to the investigator and s/he may begin participating in the study.

There is no set schedule for FDA review of protocol amendments; each review is dependent on the reviewer's workload. Therefore, the sponsor should contact the FDA project manager assigned to the IND to ascertain the review status of each amendment prior to implementation.

2. **Information amendments** [21 CFR 312.31]
Any essential information that is not included in a protocol amendment, IND safety report, or annual report must be submitted to the FDA. Examples of essential information include:

- New toxicology, chemistry, or other technical information
- Discontinuation of an investigation
- Information amendments should be submitted as necessary, but not more than every 30 days

When several submissions of new protocols, or protocol changes are anticipated in a short period, the sponsor is encouraged to include these in a single submission.

3. **IND safety/adverse events reports** [21 CFR 312.32]

**Definitions that apply to IND safety reporting requirements**

- ***Adverse event*** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
  - The sign or symptom is temporally associated with the use of the drug
  - But does not imply judgment of causality

- ***Suspected adverse reaction*** is any adverse event for which there is a reasonable possibility that the drug caused the adverse event.
  - Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the adverse event

- ***Adverse reaction*** is any adverse event caused by the drug

- ***Life-threatening adverse event or life-threatening suspected adverse reaction*** is an event that places the subject at immediate risk of death.
  - It does not include events that, if they had occurred in a more severe form, might have caused death

- ***Serious adverse event or serious suspected adverse reaction*** is an event that results in:
  - Death
  - Life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

FDA regulations require that sponsors make the causality assessment, based on information received from investigators; and indicates that the sponsor should consider both the investigator's and the sponsor's assessment when determining if an event is serious.

- ***Unexpected adverse event* or *unexpected suspected adverse reaction*** is an event that:
  - It is not listed in the investigator brochure (IB) or
  - If it is listed, it includes those events that occur with members of the class of drugs or are anticipated as part of the pharmacological properties of the drug but have not previously been observed with the investigational drug; or
  - If an investigator brochure is not required or available, it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended

**Why are IND safety reports required?**

To ensure the timely communication of significant new information about experiences with the investigational drug. Findings that suggest a significant risk would ordinarily result in a safety-related change in the protocol, ICD, IB or the conduct of the study (e.g., result in a protocol amendment).

**To whom are they submitted?**

- The FDA division that is responsible for the IND review
- All participating investigators – this includes
  - All investigators participating in clinical trials under the IND (including US and non-US sites)
  - Investigators conducting a study under their own IND for whom the sponsor provides the drug

**How should they be reported?**

- By phone, fax, or e-mail
- If the IND is in eCTD (electronic common technical document) format, the IND safety report may be submitted in this format

**What should be reported and when?**

<u>All safety reports must be reported ASAP, but no later than 15 calendar days after determining the information qualifies for reporting</u> - with the exception of <u>unexpected fatal or life-threatening suspected adverse reactions.</u>

- ***Serious and unexpected suspected adverse reaction (SUSAR)***

- Must be reported only if the SI determines there is evidence to suggest a causal relationship between the drug and the adverse event.

- ***Unexpected fatal or life-threatening suspected adverse reactions***
  - Must be reported no later than 7 calendar days after the sponsor's initial receipt of the information

- ***Findings from other studies that suggests a significant risk in humans exposed to the drug***
  - Whether or not conducted under an IND
  - Whether or not conducted by the SI
  - Includes any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies

- ***Findings from animal or in vitro testing that suggests a significant risk in humans exposed to the drug***
  - Whether or not conducted by the SI
  - Includes reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure
- ***Increased rate of occurrence of serious suspected adverse reactions***
  - A clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure
  - The sponsor should consider a variety of factors (study population, nature and seriousness of the reaction and the magnitude of the observed increase in rate)

- **Additional information that must be included in each IND safety report:**
  - All IND safety reports previously submitted to the FDA concerning a similar suspected adverse reaction
  - The significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information

**UI IRB policy**

The following events are considered reportable per UI policy and must be reported to the IRB via the Reportable Event Form (REF) in HawkIRB.

- Any **serious adverse drug event** that the PI determines to be **related** to the study drug, whether it is **unexpected or expected** that occurs in a **subject enrolled by a UI investigator**

- A serious, unexpected, suspected adverse reaction **(SUSAR)** occurs in a subject at a **non-UI site** and the event **impacts UI subjects or the conduct of the study at the UI** (e.g., results in an amendment to protocol) it meets the reporting requirements of **an unanticipated problem involving risks to subjects (UPIRTSO)**

UI investigators must submit reportable events within 10 working days of the event or

the investigator becoming aware of the event. The IRB recommends the SI attach a copy of the report that was sent to the FDA to the REF. An IRB Chair will review the REF and may request additional information.

4. **Annual reports** [21 CFR 312.33
   The SI must submit an annual progress report to the FDA within 60 days of the anniversary date that the IND went into effect. This is the date the FDA permitted the study to begin and can be found on the FDA IND Acknowledgement Notice. The expected contents of the progress report are included in the hyperlink above.

   If the due date of the annual report does not coincide with the date the IRB Continuing Review is due, the SI should describe in the first Continuing Review (CR) application that the annual report is not yet due, but the annual report will be attached at the time of the next Continuing Review. The annual report should be included on the Continuing Review Attachment category of the IRB Continuing Review form at the time of the next Continuing Review (CR). An annual report should be attached to all subsequent CRs.

5. **Withdrawal of an IND** [21 CFR 312.38]
   Sponsor-investigators must inform the FDA of the desire to withdraw an IND. All clinical investigations conducted under the IND must cease, all current investigators must be notified and all of the study drug must be returned to the sponsor or otherwise disposed of at the request of the sponsor per 21 CFR 312.58.

6. **Financial disclosure reports** [21 CFR 312.57(b)]
   Any changes to financial disclosure information must be promptly reported to the FDA during the investigation and for 1 year following completion of the study. This information does not need be reported to the IRB.

7. **ClinicalTrials.gov reporting and results** [FDAAA801]
   The Responsible Party should update their records within 30 days of a change to the protocol, the recruitment status, or completion date. Records must be updated at least every 12 months, even if nothing has changed.

   In general, results of an applicable clinical trial of a drug or biologic that is approved, licensed, or cleared by FDA must be submitted by the sponsor no later than 12 months after the primary completion date.

**B. Sponsor recordkeeping** [21 CFR 312.57]
The SI is responsible for maintaining the following records.

- **Drug accountability** [21 CFR 312.57a]
  Accurate records documenting the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

- **Financial interest** [21 CFR 312.57b]
  Documentation of any financial interests of any of the participating investigators involved in the study (see also 21 CFR 54). The sponsor- investigator is responsible for ensuring all participating investigators provide the SI with sufficient accurate financial information to allow the SI to submit complete and accurate certification or disclosure statements. The SI shall promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

**C. Sponsor record retention**
The FDA requires that the aforementioned records must be maintained: [21CFR 312.57(c)]

- During time of all research conducted under the IND and for 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated
- If no application is to be filed or if the application is not approved for such an indication, the SI is responsible for maintaining the records until 2 years after the investigation is discontinued and FDA is notified (IRB or other requirements may differ)

**D. Inspection of sponsor's records and reports** [21 CFR 312.58]
The SI must allow FDA employees access to all records and reports at their request. Drug Enforcement Administration and Department of Justice employees must be given access to records and reports involving controlled substances at their request.

## V. What are the sponsor-investigator's responsibilities *as an investigator*?

The SI has all the responsibilities of investigators in any clinical trial.

**A. General responsibilities** [21 CFR 312.60]

- Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations
- Protecting the rights, safety, and welfare of subjects under the investigator's care

**B. Assurance of IRB review** [21 CFR 312.66]
The SI is responsible for assuring that:

- A qualified IRB will be responsible for initial and continuing review and approval of the investigation
- All changes and unanticipated problems involving risk to human subjects or others are reported to the IRB
- No changes in the investigation will be made without prior IRB approval**,** except where necessary to eliminate apparent immediate hazards to human subjects

**C. Control of the investigational drug** [21 CFR 312.61]
As investigator, the SI must administer the investigational drug only to subjects under his/her direct supervision, or under the supervision of a sub-investigator responsible to the investigator. The SI must also ensure that the investigational drug is not given to any person

not authorized to receive it. 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 21 CFR 312.59.

**D. Investigator record Keeping**

Accurate documentation of the following must be maintained.

- **Case Histories** [21 CFR 312.62(b)]
  As investigator, the SI will maintain accurate case histories that record all observations and other data pertinent to the investigation on each subject who received the investigational drug and each subject who was a control in the investigation.

  Case histories include the case report forms, supporting data such as signed, dated consent forms, and medical record information 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.

- **Disposition of the Investigational Drug** [21 CFR 312.62]
  The SI is responsible for maintaining adequate records of the disposition of the drug, including dates, quantity, and use by subjects.

**E. Investigator record retention** [21 CFR 312.62]

SIs are required to maintain:

- All correspondence relating to the use of human subjects in research, as well as copies of the IRB application forms, approval notices, and signed Informed Consent Documents (ICD)
- UI policy requires that:
  - Research records that include Protected Health Information (PHI) must be kept for six years after the close of the project in HawkIRB
  - Research records that do not involve PHI must be kept for at least 3 years after the close of the study
  - Research records for VAMC studies must be kept indefinitely

**F. Inspection of sponsor-investigator's records and reports** [21 CFR 312.68]

The sponsor-investigator (SI):

- Must allow FDA employees access to all records and reports at their request
- Shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 21 CFR 312.62
- Is not required to divulge participant names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

**G. Handling of controlled substances** [21 CFR 312.69]

As investigator, the SI must take adequate precautions to ensure the safe and secure handling of the investigational drug if it is a controlled substance. This includes proper storage in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

## VI. Disqualification of a Clinical Investigator [21 CFR 312.70]

If the FDA obtains information indicating that the SI or an investigator has repeatedly or deliberately failed to comply with the regulations or has submitted false information to the FDA in any required report, the following will occur:

- The FDA will notify the investigator in writing of the complaint.
- The investigator will be given an opportunity to explain the matter in writing, or in an informal conference.
- If the investigator's explanation is not accepted, the investigator will be given an opportunity for a regulatory hearing to determine if the investigator is entitled to receive investigational new drugs.
- If, after evaluating all available information, the Commissioner of the FDA determines that the investigator has repeatedly or deliberately failed to comply with the requirements or has deliberately or repeatedly submitted false information to the FDA or the sponsor, the Commissioner will notify the investigator, the sponsor of any investigation that the investigator has participated in, and the reviewing IRBs that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.
- Each application or submission to the FDA containing data reported by the investigator who has been determined to be ineligible to receive investigational drugs is subject to examination to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation, the approval of any marketing application, or to the continued marketing of an FDA-regulated product.
- If, after eliminating unreliable data submitted by the investigator, the Commissioner determines that it is not reasonably safe to continue the investigation, the Commissioner will notify the sponsor who shall have an opportunity for a regulatory hearing.
- If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor and the reviewing IRBs of the termination. The sponsor will have an opportunity for a regulatory hearing before the FDA to determine whether the IND should be reinstated.
- If, after eliminating unreliable data submitted by the investigator, the Commissioner determines that the continued approval of the drug product cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the relevant statutes.
- An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational drugs and will conduct clinical investigations regulated by the FDA solely

in compliance with the regulations.

## VII. Expanded Access to Investigational Drugs for Treatment Use 21 CFR 312.300

Expanded access, also called compassionate use, is the use of an investigational drug outside of a clinical trial to treat a patient. It provides access to promising therapeutic agents without compromising the protections of human subjects or the thoroughness and scientific integrity of product development and marketing approval.

Three criteria must be met for the FDA to approve this use.

1. The patient must have a serious or life-threatening condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition
2. The potential benefit to the patient justifies the potential risks of the treatment use and the risks are not unreasonable in the context of the disease or condition to be treated
3. Providing the investigational drug for this use must not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of this use.

An expanded access IND is available to individual patients, intermediate size patient populations and larger populations. The FDA requires an IND submission for each of these three types of expanded access. The submission may be a new IND or a protocol amendment to an existing IND. Submission requirements are outlined at 21CFR 312.305(b). Sponsors and investigators of expanded access use must comply with the responsibilities of all IND sponsors and investigators to the extent that the responsibilities apply to expanded access use 21 CFR 312.305(c).

## VIII. Additional References

The following links provide additional information:

- Code of Federal Regulations 21 CFR 50 - Protection of Human Subjects
- Current Good Manufacturing Practice In Manufacturing, Processing, Packing or Holding of Drugs; General 21 CFR 210
- Current Good Manufacturing Practice for Finished Pharmaceuticals 21 CFR 211
- Drugs for Human Use 21 CFR 314
- Bioavailability and Bioequivalence Requirements 21 CFR 320
- Over-The-Counter (OTC) Human Drugs Which are Generally Recognized as Safe and Effective and Not Misbranded 21 CFR 330
- Biologics Licensing 21 CFR 601

**Human Subjects Office**
**319-335-6564 irb@uiowa.edu**

## Appendix 1 – IND Checklist

### IND Submissions to FDA

For detailed description of FDA requirements
☐See 21 CFR 312.33 for content and format of IND application

☐1571 (IND cover sheet) is required

Upon initial IND submission:
- In Section 10, the serial number should be '000' (see IND Handout pg 3)
- In Section 11, only the 'Initial Investigational New Drug Application (IND)' box should be checked

Upon subsequent submissions:
- The serial number should increase consecutively in the order of submission (e.g.,001, 002)
- If more than one type of information is included in a submission, all boxes that correspond to the type of submission should be checked

☐ClinicalTrials.gov registration – see HSO website for more information
- Applicable clinical trials include those involving a FDA IND
- At the UI, the Responsible Party of an investigator-initiated study is the PI, known as sponsor-investigator
- Federal deadline - no later than 21 days after enrollment of first participant or Publishing deadline
- International Committee of Medical Journal Editors (ICMJE) deadline prior to the enrollment of the first subject
- After submission to ClinicalTrials.gov staff review and approve the information
- Contact the ct-gov@uiowa.edu to get a username for ClinicalTrials.gov Protocol Registration and Results System (PRS)
- Provide the National Clinical Trial number (NCT#) in HawkIRB Section VII.B.1 once the study is registered on ClinicalTrials.gov

☐Form FDA 3674 (ClinicalTrials.gov Certification of Compliance) or other form of certification
- Must accompany certain human drug and biologic product applications to the FDA (New IND applications and new protocols submitted as an amendment to the IND)

### IND Submissions to IRB

**IND Application should include:**

☐Copy of initial 1571
☐Protocol
☐Investigator Brochure
☐Documentation from FDA (that study may proceed or date application was received)
☐1572 is optional
*Include the 1571 & FDA documentation in the 'Sponsor Documentation' category on Attachment page

If the IRB determines that an IND is required, but the FDA disagrees, attach documentation of the FDA's determination that an IND is not needed (see IND Handout pg 4).

### Reporting requirements to FDA

Once the IND is in effect, submit the following to the FDA.

☐Protocol Amendment
- New protocol - any study not contained in the IND application
- Protocol changes – changes/additions to protocol
- New investigator – within 30 days of addition of investigator

☐Information Amendment - for any essential information not included in item 1 above

☐IND safety reports – (see IND Handout pgs 7-9)

☐Annual reports – within 60 days of the anniversary date that he IND went into effect

☐Notice of intent to withdraw IND

☐Financial disclosure information- changes must be during/for 1 year after completion of study

☐Certification of Compliance Form (FDA Form 3674) – for new protocols submitted as an amendment to the IND application

☐Clinical Trials.gov reporting and results
- Update records - within 30 days of a change in recruitment status, or completion date. Protocol amendments/other updates must be made every 12 months
- Submit results - no later than 1 year after the primary completion date

## Reporting requirements to IRB

The same information that is submitted to the FDA must be submitted to the IRB, but the format and the timing of the submissions will vary.

### Modifications

Should describe:

☐Protocol Amendments, including new protocols, protocol changes and new investigators

☐Information Amendments

☐Notice to withdraw IND

Should include:

☐Corresponding 1571 documenting a change in serial number & describing the type of submission (upload on top' of previous 1571 (see IND Handout pg 3)

☐Documentation of FDA submission and the date

**Timing** - Submit the IRB modification at the time of the IND submission to the FDA

### Addition of New Protocol

If a new protocol is added to an IND application, the IRB expects the IND holder to maintain:

☐One overall IRB application containing
- The entirety of the IND application
- A full history of the initial submission
- All amendments that are submitted to the FDA

☐A separate IRB application for each ancillary study to be conducted at the UI that
- Includes the required IND information relevant to the ancillary study only
- References the IRB ID# of the main IND study in Section I.4

## Reportable Event Forms (REFs)

Are used to report IND Safety/adverse event reports that meet the following definitions:

☐A serious adverse drug event that the PI determines to be related to the study drug, whether it is **unexpected or expected** that occurs in a subject enrolled by a UI investigator

☐A serious, unexpected, suspected adverse reaction (SUSAR) occurs in a subject at a non-UI site and the event impacts UI subjects or the conduct of the study at the UI (e.g., results in an amendment to protocol) it meets the reporting requirements of an **unanticipated problem involving risks to subjects (UPIRTSO)**

☐Attach a copy of IND safety report that was sent to FDA to the REF

**Timing** – Submit within 10 working days of the event or the investigator becoming aware of the event.

## Annual Reports

Required at the time of Continuing Review (CR).

☐If the due date of the first annual report does not coincide with the date the IRB Continuing Review is due, describe in the CR that the annual report is not yet due

☐An annual report is expected to be attached to all subsequent CR applications

## Financial Disclosure

Information is reported via eCOI system and not to the IRB.

### FDA recordkeeping requirements for sponsors-investigators

**The FDA requires that you maintain the following documents:**

**Record type**

☐Drug accountability and disposition
☐Case histories
☐Financial interest records
☐Subject case histories

**Duration**

☐During and for 2 years after the date a marketing application is approved for the drug for the indication for which it is being investigated

☐If no application is to be filed or if the application is not approved for such an indication, maintain the records until 2 years after the investigation is discontinued and FDA is notified (IRB or other requirements may differ)

### IRB recordkeeping requirements for sponsors-investigators

**The IRB expects that you retain the following:**

**Record type**

☐All IRB application forms, approval notices, signed Informed Consent Documents
☐All correspondence related to use of human subjects in research

**Duration**

☐Research records that do not involve Protected Health Information (PHI) must be kept for 3 years after the close of the study in HawkIRB

☐Research records involving PHI must be kept for 6 years after the close of the project in HawkIRB

☐Research records for VAMC studies must be kept indefinitely

The IRB recommends the sponsor-investigator maintain all correspondence with the FDA.