**Investigational Drugs and Biologics**

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.

**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

**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.

**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 factors 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.

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.

**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-HSR.  The FDA may over-rule the IRB regarding the need for an IND.  The School of Medicine Clinical Trials Office (SOM-CTO) staff is available to assist the investigator in contacting the FDA and writing a position statement to the IRB-HSR regarding the need for an IND.  If it is determined that an IND is required, the SOM-CTO personnel are also available to advise researchers regarding the application preparation.  In addition, the IRB requires researchers to obtain SOM- CTO approval for these types of studies.  The SOM-CTO review includes careful attention to the Data Safety Monitoring Plan, and Data Collection Forms.   This review must take place before the IRB will allow subjects to be enrolled.

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.

If a UVA faculty member is the principal investigator on an IND or IDE, the IRB-HSR will require an approval from the School of Medicine Clinical Trials Office prior to subjects enrolling in the protocol. Prior to granting approval, the SOM CTO will conduct of review of various items with special focus on areas of FDA interest such as- inclusion/exclusion criteria, safety plan , endpoints, data collection process and the communication plan with other sites , if multi-site. The staff of the SOM CTO will also review Sponsor responsibilities with the PI. Sponsor responsibilities for an IND are found at 21CFR312. Sponsor responsibilities for an IDE are found at 21CFR812.

**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).

**Maintaining an IND**

When the UVA 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 UVA 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 1572 and current dated and signed CVs.
   * each time a new investigator is added. An amended 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 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 should be submitted.)

1. The PI is expected to keep all data secure.
2. All data is expected to verifiable. This means that adequate source documentation and data collection forms are maintained. Please refer to the SOM-CTO and FDA websites for additional information. Links to both are available from the IRB-HSR website.

# 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. 

**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 School of Medicine Clinical Trials Office (SOM CTO) 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.

**Multi-site trial:**

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

A common protocol is required for all multi-site trials. See [Multi-Site Studies](https://research.virginia.edu/irb-hsr/multi-site-studies) for additional information. At the time of initial review the IRB will require an approval from the SOM CTO who will assess the 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 UVA 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 the University of Virginia 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 UVA IRB's continuing approval of the research.

If a UVA faculty member is the principal investigator on an IND or IDE, the IRB-HSR will require an approval from the School of Medicine Clinical Trials Office prior to subjects enrolling in the protocol. Prior to granting approval, the SOM CTO will conduct of review of various items with special focus on areas of FDA interest such as- inclusion/exclusion criteria, safety plan, endpoints, data collection process and the communication plan with other sites , if multi-site. The staff of the SOM CTO will also review Sponsor responsibilities with the PI. Sponsor responsibilities for an IND are found at 21CFR312. Sponsor responsibilities for an IDE are found at 21CFR812