Yale University Institutional Review Boards

IRB Policy 600 Use of Investigational New Drugs, Devices and Biologics in Human Research

<table>
<thead>
<tr>
<th>Responsible Office</th>
<th>Office of Research Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responsible Official</td>
<td>Institutional Review Board Executive Chair</td>
</tr>
<tr>
<td>Effective Date</td>
<td>12/4/09</td>
</tr>
<tr>
<td>Last Revision</td>
<td>11Dec2017</td>
</tr>
</tbody>
</table>

Policy Sections ............................................................................................................................................. 6
600.1 Investigational New Drugs (INDs) ................................................................................................................. 6
600.2 Investigational Device Exemptions (IDEs) ................................................................................................. 8
600.3 Investigator-Held IND or IDE (Sponsor-Investigator) ............................................................................... 10
600.4 Expanded Access use/Treatment Use of an Investigational or Unlicensed Drug or Device ........................................ 11
600.5 Emergency Use of an Investigational or Unlicensed Drug or Device ............................................................ 11
600.6 Compassionate Use of an Investigational or Unapproved Device .............................................................. 12
600.7 Use of Biologic in Research ..................................................................................................................... 12

Related Information ............................................................................................................................................. 12

Scope

This policy applies to all investigators conducting human research under an investigational new drug (IND) application, investigational device exemption, (IDE) or a Biologics License Application (BLA).

Policy Statement

Investigators who conduct human research regulated by the Food and Drug Administration (FDA) under 21 CFR §50 and §56 are required to know and comply with all relevant FDA regulations governing the use of investigational drugs, devices, biologics or other test articles. Under FDA regulations (21 CFR §312), research that involves the use of a drug other than the use of a marketed drug in the course of medical practice must be conducted under an investigational new drug (IND) application, unless the protocol meets one of the five exemptions from the requirement for an IND. Research that is conducted to determine the safety or effectiveness of a device must have an Investigational Device Exemption (IDE, 21 CFR §812) issued by the FDA, unless the device meets the requirements for an abbreviated IDE or the protocol meets one of the five exemptions from the requirement for an IDE. Research that involves the use of a biologic must be conducted under 21 CFR parts §600, §601, and §610.

Reason for the Policy

This policy helps to ensure that the regulatory requirements for the conduct of clinical investigations of drugs and devices in human research are known and complied with when Yale investigators conduct research under an IND or IDE. It is also intended to encourage the discovery and development of useful drugs and devices intended for human use while ensuring the protection of public health and safety as well as ethical standards. An accepted IND application or approved IDE permits a drug or device that otherwise would be required to comply with a performance standard or to have premarket approval by FDA to be shipped lawfully for the purpose of conducting investigations of that drug or device.

Definitions

Biologics
A biological or related product, regulated by the FDA, including blood, vaccines, allergens, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals and microorganisms). Studies of unlicensed biologics are regulated according to the Investigational New Drug (IND) regulations (21 CFR §50.312), except in some cases when the biologic is in a combination product with a medical device. FDA regulates biologics general use and licensing under 21 CFR §600 and §601. (42 U.S.C. 262 of the Public Health Service Act). Following initial laboratory and animal testing that show that investigational use in humans is reasonably safe, biological products (like other drugs), can be studied in clinical trials in humans under an investigational new drug application (IND) in accordance with the regulations at 21 CFR §312. If the data generated by the studies demonstrate that the product is safe and effective for its intended use, the data are submitted as part of a marketing application.

Clinical Investigation
Any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to the FDA under section 505(i) or 520 (g) of the Federal Food, Drug and Cosmetic Act (FD&C Act),
or need not meet the requirements prior to submission to the FDA under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigations are deemed synonymous for the purposes of this part. (See 21 CFR §56.102).

**Compassionate Use**

For purposes of this policy, compassionate use refers to the treatment of a seriously ill patient using an unapproved test article where no other treatments are satisfactory. Such use of an investigational drug, biologic, or device actually falls into one of the following treatment mechanism and is allowed only after prior review and approval by the IRB, and in most circumstances prior approval by the FDA as well. Prior IRB approval is needed even if only one patient is to be treated under the following mechanisms:

**Expanded Access**

- **Treatment INDs or Individual Patient access to Investigational Drugs/devices for Serious Diseases:** These mechanisms are primarily intended to give seriously ill patients access to experimental drugs or devices where no comparable or satisfactory alternative treatment is available. Although the tests article sponsor is expected to continue conventional clinical trials and pursue marketing approvals with due diligence, expanded access studies involve systematic use of experimental treatments, and, with rare exceptions, require the same review and approval as research, including both IRB approval and FDA approval in the form of an Investigational Device Exemption (IDE) (medical device) or an Investigational New Drug (IND) (drug/biologic).

- **Open Protocols (Parallel Track, Open label Protocol, Open Label IND) or Continued Access IDEs:** Uncontrolled studies, typically used when controlled trials have ended and treatment is continued so the subjects may continue to receive the benefits of the test article until marketing approval is obtained. Informed consent and prior IRB approval are required.

**Devices**

Clinical investigations of devices are subject to the Investigational Device Exemption (IDE) regulations at 21 CFR §812.

An approved IDE permits a device that is not approved (via premarket authorization (PMA)) or cleared to market (via 510K) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk devices must have an IDE issued by FDA before they can be shipped. Nonsignificant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a nonsignificant risk device.

Research with devices falls into three (3) categories:

- Investigations of significant risk devices to determine safety and effectiveness of the device
- Investigations of Nonsignificant risk devices to determine the safety and effectiveness of the device
- Investigations exempted under the regulations

See:


Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR §812, and in some instances are eligible for IRB review according to the expedited procedure.

**Significant Risk Device Research**

Applications for research on the use of a significant risk device must be accompanied by documentation from the FDA that includes a valid IDE number. The IDE number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IDE numbers may not be validated with a device manual (which may serve multiple IDEs).

**Nonsignificant Risk Device Research**

When research is conducted to determine the safety or effectiveness of a device, the organization confirms that the device fulfills the requirements for an abbreviated IDE (21 CFR §812.2(b)(1)):

- The device is not a banned device
• The sponsor labels the device in accordance with 21 CFR §812.5
• The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
• The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator’s care, consent under 21 CFR §50 and documents it, unless documentation is waived;
• The sponsor complies with the requirements of 21 CFR §812.46 with respect to monitoring investigations
• The sponsor maintains the records required under 21 CFR §812.140(b) (4) and (5) and makes the reports required under 21 CFR §812.150(b) (1) through (3) and (5) through (10);
• The sponsor ensures that participating investigators maintain the records required by 21 CFR §812.140(a)(3)(i) and makes the reports required under 21 CFR §812.150(a) (1), (2), (5), and (7); and
• The sponsor complies with the prohibitions in 21 CFR §812.7 against promotion and other practices.

If the investigator applies to the IRB for a nonsignificant risk determination for a device study, but the IRB determines that the device is significant risk, the IRB shall notify the investigator and the sponsor, if appropriate. The sponsor must apply to the FDA for its determination regarding the necessity for an IDE.

Exempt Device Research
Clinical research investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from IDE regulations must fall into one of the following categories (21 CFR §812.2(c)):

• A device legally marketed in the US that is used or investigated in accordance with the indications in the FDA-approved labeling.

• A diagnostic device (that is, an in vitro diagnostic device) if the testing:
  o Is noninvasive
  o Does not require an invasive sampling procedure that presents significant risk,
  o Does not by design or intention introduce energy into a subject, and
  o Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

• A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety and effectiveness and does not put subjects at risk.

• A custom device as defined in 21 CFR §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

• A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with indications in labeling in effect at that time.

• A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that the Food and Drug Administration (FDA) has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling the FDA reviewed under subpart E of part 807 in determining substantial equivalence.

Human Subject or Human Participant
45 CFR §46 (Common Rule definition) –
*A living individual about whom an investigator (whether professional or student) conducting research obtains either (1) Data through intervention or interaction with the individual; or (2) identifiable private information.

*Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes.

*Interaction includes communication or interpersonal contact between investigator and subject.

*Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific
purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

21 CFR §50.3(g) and 21 CFR §56.102(e) (Food & Drug Administration definition) – An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

A subject may be either a healthy human or a patient. Specifically in regard to investigational device studies, subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used, or as a control. A subject may be in normal health or may have a medical condition or disease.

Experimental Subject (for Department of Defense-sponsored research)
Research Involving a Human Being as an Experimental Subject: An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction (32 CFR §219.102 (f), reference(c)). Examples of interventions or interactions include, but are not limited to, a physical procedure, a drug, a manipulation of the subject or subject’s environment, the withholding of an intervention that would have been undertaken if not for the research purpose.

Immediately Life-Threatening Disease
A stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Investigational New Drug (IND) application
An investigational new drug application (IND) is synonymous with “Notice of Claimed Investigator Exemption for a New Drug”. An investigational drug must have an IND before it can be shipped, unless it meets one of the exemptions outlined in 21 CFR §312.2.

Applications for research on the use of a drug, unless that research is exempt from IND regulations must be accompanied by documentation from the FDA that includes a valid IND number. The IND number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IND numbers may not be validated with an Investigator Brochure (IB) (which may serve multiple INDs).

As stated in 21 CFR §312.2(b)(1), clinical investigations of a drug product is exempt from the IND regulations if the drug is lawfully marketed in the United States and all of the following are true:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in labeling for the drug;
(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with the use of the drug product;
(iv) the investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent sent forth in part 50; and
(v) The investigation is conducted in compliance with the requirements of 312.7 (Promotion and charging for investigational drugs).

As stated in 21 CFR §312.2(b)(2), a clinical investigation involving an in vitro diagnostic biological product listed in above in (b)(2)(ii) of this section is exempt from the regulations if all of the following are true:

(a) it is intended to be used in a diagnostic procedure that confirms the diagnosis is made by another, medically established, diagnostic product or procedure and
(b) it is shipped in compliance with 312.160

Under 21 CFR §312.2(b)(2)(ii) the following products are exempt from the requirements of an IND: (a) blood grouping serum, (b) reagent red blood cells, and (c) anti-human globulin.
Additionally, a clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR §312 if the investigation does not otherwise require submission of an IND. Clinical investigations that are exempt from IND regulations still require IRB review and approval.

IND Types:

**Investigator IND (Sponsor-Investigator)**

An Investigator IND is submitted to the FDA by an investigator who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. An investigator 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.

**Treatment IND**

A treatment IND is submitted to the FDA to make promising new drugs available to desperately ill patients as early in the drug development process as possible. FDA will permit an investigational drug to be used under a treatment IND if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease in its later stage of development or if there is no alternative drug or therapy available to treat that stage of the disease in the intended individuals.

**Emergency Use IND**

The 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 the regulations. 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. Emergency and Treatment INDs are sometimes referred to as "Compassionate Use" INDs, but the term "Compassionate Use" is not in the IND regulations.

**IND Categories:**

**Commercial**

These are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product.

**Expanded Access Programs**

Refers to the use of an investigational drug outside of a clinical trial by patients with serious or life-threatening conditions who do not meet the enrollment criteria for the clinical trial in progress. This type of access may be available, in accordance with United States Food and Drug Administration (FDA) regulations, when it is clear that patients may benefit from the treatment, the therapy can be given safely outside the clinical trial setting, no other alternative therapy is available, and the drug developer agrees to provide access to the drug. The FDA refers to such a program as an expanded access program (EAP). EAPs can be leveraged in a wide range of therapeutic areas. (Including HIV/AIDS and other infectious diseases, cancer, rare diseases, and cardiovascular diseases, to name a few.)

**Single Patient Expanded Access IND 21 CFR §312.310**

The FDA may permit an Investigational drug to be used for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments.

**Expanded Access IND -Intermediate size patient population (~10 to 100) 21 CFR §312.315**

When the FDA receives a significant number of requests for individual patient expanded access to an investigational drug for the same use, they may ask the trial sponsor to consolidate these requests, creating an intermediate-size group.

**Expanded Access Treatment IND or Treatment protocol 21 CFR §312.320**

The investigational drug will be used for widespread treatment use.

**Off-Label**

Use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label use requires an IND or IDE application. (See FDA “Off-Label and Investigational Use of Marketed Drugs, Biologics, and Medical Devices – Information Sheet [http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm))
Research
45 CFR §46.102(d) (Common Rule – Subpart A) –
“A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to
generalizable knowledge. Activities, which meet this definition, constitute research for purposes of this policy, whether or
not they are conducted or supported under a program, which is considered research for other purposes.

21 CFR §50.3(g) and 21 CFR §56.102(e) (Food & Drug Administration) –
Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for
prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to
requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of
which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an
application for a research or marketing permit. The term does not include experiments that are subject to the provisions of
part 58 of this regulation, regarding nonclinical laboratory studies.

Significant Risk (SR) Device
A device that presents a potential for serious risk to the health, safety, or welfare of a subject and 1) is intended as an
implant, or 2) is used in supporting or sustaining human life, or 3) is of substantial importance in diagnosing, curing,
mitigating or treating a disease, or otherwise prevents impairment of human health, or 4) otherwise presents a potential
for serious risk to the health, safety, or welfare of a subject.

Sponsor-Investigator
Sponsor-investigator is an individual who both initiates and actually conducts, alone or with others, a clinical investigation,
i.e., under whose immediate direction the investigational drug or device is administered, dispensed, or used. The term
does not, for example, include a corporation or agency. The obligations of a sponsor-investigator include those of an
investigator and those of a sponsor.

Test Article
Any drug (including a biological product for human use), medical device for human use, human food additive, color
additive, electronic product, or any other article subject to regulation under the Act or under sections 351 and 354-360F of
the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

Policy Sections

600.1 Investigational New Drugs (INDs)
An investigational new drug (IND) application is required for investigational or experimental drugs if the drugs are
being used for the purpose of developing information about their safety or efficacy. Approved, marketed drugs
may also require an IND if the proposed use in research is different from the previously FDA-approved use, or
administered by an unapproved route or method of delivery or an altered dosage. The IND goes into effect 30
days after the FDA receives the IND, unless the sponsor receives earlier notice from the FDA. The intended use
of an approved drug may be exempt from IND application requirements under certain conditions, below.

Exemption from IND Requirements
The clinical investigation of a marketed drug or biologic does not require submission of an IND if the drug is
lawfully marketed in the United States and all six of the following conditions are met:

(1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant
change in the labeling for the drug;

(2) it is not intended to support a significant change in the advertising for the product;

(3) it does not involve a route of administration or dosage level, use in a 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) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56
and 50, respectively];

(5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR
§312.7]; and

(6) it does not intend to invoke 21 CFR §50.24 for the exception from informed consent requirements for
emergency research.
In addition, exemption from IND requirements exists if the following conditions are met:

1. The clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
   - Blood grouping serum.
   - Reagent red blood cells.
   - Anti-human globulin.

2. The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.

3. The diagnostic test is shipped in compliance with 21 CFR §312.160.

Or, if the following condition is met:

A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.

**IRB Determinations**

The fully convened IRB reviews human research protocols conducted under an IND in accordance with Policy 100 IRB Review. For studies to be conducted under an IND and not deemed exempt by the IRB as described below, investigators are required to produce documentation from the FDA indicating the IND number, which the IRB will match with information provided in the protocol submitted for review to ensure consistency. Study-related activities that directly involve human subjects (for example, recruiting, obtaining consent, and screening participants) will not be approved by the IRB until the IND or official communication from the FDA indicating its exemption determination is obtained.

In the case of studies involving investigational drugs for which an IND has not been obtained, the investigator should justify to the IRB why exemption is appropriate. In this case, the IRB will make an exemption determination based on reviewing the proposed use of the drug in light of the exemption criteria, the investigator’s statements, and its knowledge of relevant scientific information. The IRB’s determination may be concurrence that an IND is not required, or requirement that the investigator file an IND with the FDA, or requirement that the investigator obtain an exemption determination from the FDA. The IRB’s determination is generally driven by consideration of item (3) above. That is, if it is determined that the research involves some new aspect that may significantly increase risks over what is already known about the use of the drug, it is likely that an IND will be required.

**Investigator Responsibilities**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. If the investigational drug is subject to the Controlled Substances Act [http://www.deadiversion.usdoj.gov/21cfr/21usc/index.html], the investigator shall take adequate precautions, including storage of the investigational drug 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. An investigator shall obtain the informed consent of each human subject to whom the drug is administered, except when an exception to the requirements for informed consent is met.

Investigators are also responsible for the following (21 CFR §312 Subchapter D):

1. administering the drug only to subjects under the investigator’s personal supervision or under the supervision of a co-investigator responsible to the investigator;
2. supplying the drug only to persons authorized to receive it;
3. maintaining adequate records for the disposition of the drug (dates, quantity, and use by subjects);
4. returning unused supplies to the sponsor (agency, industry or investigator) or otherwise providing for the disposition in accordance with the direction of the sponsor;
5. maintaining adequate and accurate case histories on each individual receiving the drug or employed as a control (all observations and other data pertinent to the investigation including case report forms and
supporting data (source documents, e.g., signed and dated consent forms, medical records including progress notes, hospital charts and nurses notes);

6. retaining records for 2 years after either the date a marketing application is approved for the drug for the indication under investigation, or, if no application is to be filed or if the application is not approved, until 2 years after the investigation is discontinued and FDA is notified;

7. submitting progress reports and safety reports to the sponsor and IRB;

8. providing financial disclosures to the sponsor and the IRB;

9. storing drugs properly and securely;

10. obtaining IRB and FDA review and approval prior to initiating the research (including the consent process) and prior to initiating any changes to the approved research; and

11. permitting authorized individuals (e.g., IRB personnel, University auditing personnel, FDA personnel, federal Drug Enforcement Agency (DEA) personnel) to have access to and to copy relevant records.

Additional requirements include a commitment by the investigator that he or she:

1. Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after securing IRB approval and notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

2. Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent regulatory requirements;

3. Will personally conduct or supervise the described investigation(s);

4. Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent and IRB review and approval are met;

5. Will report to the IRB and the sponsor adverse experiences that occur in the course of the Investigation(s) in accordance with Yale University Policy 720 on Adverse Event Reporting, and 21 CFR §312.64;

6. Has read and understands the information in the investigator’s brochure, including the potential risks and side effects of the drug;

7. Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments; and

8. Will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

In the event that a Yale PI is also the sponsor of the IND, the PI must comply with requirements of sponsor-investigators as described below and at http://info.med.yale.edu/hrpp/sponsorinvest.html (IND Sponsor-Investigator Guidance 600 GD. 1.)

600.2 Investigational Device Exemptions (IDEs)
Under FDA regulations (21 CFR §812), research that is conducted to determine the safety or effectiveness of a device must have an IDE issued by the FDA, unless the device meets the requirements for an abbreviated investigational device exemption (IDE) or the protocol meets one of the five exemptions from the requirement for an IDE that relate to use in humans (see 21 CFR §812.2). The clinical study of a new indication for an already marketed, FDA-approved device falls under the IDE regulations as well.

Significant Risk or Non-Significant Risk Devices
The FDA established three regulatory classes for medical devices based upon the degree of control necessary to assure that the various types of devices are safe and effective. Devices are classified depending upon their intended use as well as the risk the device presents to humans. FDA guidance for determination of classification of devices and regulatory control is located at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm#introduction. The sponsor of the device will make the initial determination of whether the device presents a significant risk (SR) or non-significant risk (NSR). A NSR device study is one that does not meet the definition of a SR study. NSR device studies are not necessarily minimal risk studies. For a list of NSR devices, see http://www.fda.gov/oc/ohrt/irbs/devices.html#risk.
For SR device studies, the FDA must approve an IDE application submitted by the sponsor, and the IRB must approve the study before it may commence. SR device studies require review of the full board. In the event that a Yale PI is also the sponsor of the IDE, the PI must comply with requirements of sponsor-investigators as described below.

NSR device studies do not require submission to the FDA. These studies must comply with the abbreviated regulations set forth in 21 CFR §812.2(b). Unless otherwise notified these NSR devices are considered to have an approved Investigational Device Exemption (IDE) if the sponsor fulfills the regulatory requirements of 21 CFR §812.2(b). While exempt from FDA approval, NSR studies must receive IRB approval prior to commencing. NSR studies generally will require full board review but may be approved through the expedited review procedure if the study falls within a designated approvable category and is minimal risk.

Device Categories

To assist Medicare (CMS) in determining coverage for such devices, and thereby assisting IRBs in understanding subject economic responsibilities for such devices, the FDA further assigns each device with an FDA-approved IDE into one of two categories: Category A – Experimental (safety and efficacy not yet established), and Category B – Investigational; Non-experimental (underlying questions on safety and efficacy have been resolved). See Definitions for complete descriptions of device categories.

IRB Determinations

The fully convened IRB reviews human research protocols conducted under an IDE in accordance with Policy 100 IRB Review. Investigators are required to produce documentation from the FDA indicating the IDE number, which the IRB will match with information provided in the protocol submitted for review to ensure consistency. In the case of studies involving investigational devices for which an IDE has not been obtained, the investigator should justify to the IRB why exemption is appropriate. In this case, the IRB will make an exemption determination based on reviewing the proposed use of the device in light of the exemption criteria, the investigator’s statements, and its knowledge of relevant scientific information, it is likely that an IDE will be required.

In assessing the risk level of a device, the IRB will consider information contained within the protocol application or investigator’s brochure, such as a description of the device and its proposed use, nature of the harm that may result from the use of the device or from procedures required for use of the device (e.g., surgical implants), reports of prior investigations conducted with the device, the proposed investigational plan, a description of subject selection criteria and monitoring procedures. The IRB should be provided with the sponsor’s risk assessment and rationale for its determination as NSR. The sponsor must provide the IRB with the FDA’s assessment of the device’s risk if such an assessment has been made. The IRB may also choose to consult directly with the FDA.

The IRB will make the final determination for NSR devices. If the IRB disagrees with the sponsor and designates the device as SR, the IRB will require that the sponsor submit to the FDA for an IDE. The study will not be approved by the IRB until the IDE is obtained or official communication from the FDA indicating its determination of NSR is obtained. The investigator will be informed of the IRB’s determination in writing and the investigator must inform the sponsor.

Investigator Responsibilities

The principal investigator of a device study is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations; for protecting the rights, safety, and welfare of subjects under the investigator’s care; and for the control of devices under investigation. An investigator also is responsible for ensuring that informed consent is obtained in accordance with regulatory requirements.

If any investigational devices are used, or investigational procedures performed, in a Yale New Haven Hospital Operating Room, then investigators are required to complete an YNHH OR New Product/Trial Request Form. The OR Materials Manager should be contacted at 203-688-8912 for more information on this requirement. Furthermore, per YNHH policy, the request must be reviewed and approved by the Operating Room New Technology Committee before patients may be scheduled. The notice of approval from the OR New Technology Committee must be submitted to the IRB for the protocol file.

Investigators are also responsible for ensuring the following (21 CFR §812.110, Subparts E and G):
1. obtain appropriate approvals (IRB, YNHH, FDA) prior to obtaining consent and enrolling any subjects;
2. make financial disclosures to the sponsor and the IRB;
3. supervise the device use, and ensure that the device is used only with subjects under the investigator’s supervision;
4. supply the device to only individuals authorized under the regulations;
5. upon completion or termination of a clinical investigation, or the investigator’s part of an investigation, or at the sponsor’s request, return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs;
6. permit authorized persons (e.g., IRB staff, FDA staff) to inspect and copy records relating to the investigation; if authorized, permit authorized persons (e.g., IRB staff, FDA staff) to enter and inspect any establishment where devices are held (manufactured, processed, packed, installed, used, or implanted, or where records of results from use of devices are kept);
7. maintain adequate records including: correspondence with another investigator, an IRB, the sponsor, a monitor, or the FDA;
8. records of receipt, use or disposition of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark, the names of all persons who received, used, or disposed of each device, why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of;
9. each subject’s case history and exposure to the device (include the case report forms and supporting data including, for example, the signed and dated consent forms, medical records including progress notes, adverse event reports);
10. the protocol and records of any deviations from the protocol;
11. and any other records required by the FDA or IRB or relevant to the study;
12. submit reports of unanticipated adverse device effects to the IRB within 48 hours of discovery, in accordance with Adverse Event Reporting Policy 720, and to the sponsor as soon as possible but within 10 days of becoming aware of the event;
13. submit a report to the sponsor within 5 days of any withdrawal of IRB approval;
14. submit progress reports to the IRB, sponsor, and monitor at least annually.

Investigators should refer to [http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049864.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049864.htm) for additional information on responsibilities in conducting significant risk device investigations.

**600.3 Investigator-Held IND or IDE (Sponsor-Investigator)**

Investigators who hold an investigational new drug application (IND) or investigational device exemption (IDE) are required to follow the FDA’s requirements for sponsors in addition to those for investigators.

**Additional general requirements for IND holders:**

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug. Additional specific responsibilities of sponsors are described in 21 CFR §12 Subpart D—Responsibilities of Sponsors and Investigators. (See also [http://info.med.yale.edu/hrpp/sponsorinvest.html](http://info.med.yale.edu/hrpp/sponsorinvest.html), or IND Sponsor-Investigator Guidance 600 GD. 1.)
Additional general requirements for IDE holders:

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation. Additional responsibilities of sponsors are described in 21 CFR §812 Subparts B (Application and Administrative Action) and G (Records and Reports).

Sponsor-Investigators should refer to http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm049859.htm for additional information on responsibilities as holders of an IDE.

600.4 Expanded Access use/Treatment Use of an Investigational or Unlicensed Drug or Device

An investigational drug or device may be used in a research study (clinical investigation) for the treatment (or diagnosis) of a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative drug, device, or other therapy is available. During the course of the research study, it may be appropriate to use the drug or device in the treatment of a patient not able to enroll in the research, in accordance with a specially developed treatment protocol or treatment IND or IDE (21 CFR §312.00 (is the general reg. with 310,315,320 specifying each subset) 312.34 and 812.36).

The provider in this case is regarded as a treating clinician for the patient, and not an investigator for a research participant. The clinician is required to develop and submit a specific protocol application and associated consent document for full IRB review and approval prior to the specifically intended single-patient treatment use of an IND or IDE. The clinician should seek FDA approval for the treatment use of an IND or IDE before requesting IRB review. Treatment may begin 30 days after FDA receives the treatment IND or IDE submission, or on earlier notification by FDA that the treatment use described in the protocol may begin, unless FDA notifies the sponsor in writing earlier than the 30 days that the treatment use may not begin.

Criteria for Treatment IND or Treatment IDE

FDA will permit an investigational drug or device to be used for a treatment use under a treatment protocol or treatment IND (or IDE) if the clinician/investigator provides sufficient evidence of safety and effectiveness to support such use, or provides reasonable basis that the drug or device may be effective for its intended use in its intended patient population; or would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury. The clinician/investigator must demonstrate that:

(i) The drug (or device) is intended to treat (or diagnose) a serious or immediately life-threatening disease (or condition);

(ii) There is no comparable or satisfactory alternative drug (or device) or other therapy available to treat (or diagnose) that stage of the disease (or condition) in the intended patient population;

(iii) The drug (or device) is under investigation in a clinical trial under an IND in effect for the trial (or for the same use under an approved IDE), or all clinical trials have been completed; and

(iv) The sponsor of the clinical trial (or investigation) is actively pursuing marketing approval (or clearance) of the investigational drug (or device) with due diligence.

To ensure that appropriate safeguards are in place, treatment use of an investigational drug (or device) is conditioned on the sponsor and clinician/investigator complying with the safeguards of the IND (or IDE) process, including the regulations governing informed consent and prior review and approval by the IRB, and the provisions of 21 CFR §312 (or 21 CFR §812) that include distribution of the drug (or device) through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND (or IDE) safety reports.

600.5 Emergency Use of an Investigational or Unlicensed Drug or Device

When a clinician conducts an emergency use of a test article (e.g., investigational drug or device) in a life-threatening situation without prior IRB review, the activity is still regarded as research under FDA regulations and the patient is regarded as a research subject, and the FDA may require data from an emergency use of a test article in a life-threatening situation to be reported in a marketing application. FDA regulations permit the emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days after it is used. (See 21 CFR §56.104(c).) The IRB will determine that the circumstances of the emergency use met FDA regulations. (Note that any subsequent use of the test article for this purpose at the institution is subject...
to prior IRB review.) Whenever possible, the treating clinician should notify one of the Chairs of the IRB of his/her intent to utilize an investigational drug or device for an emergency therapeutic or diagnostic reason at least 24 hours prior to the planned date of the first administration of the drug or use of the device. Review by the IRB Chair for such use is specific and limited to the individual patient. (For more information on procedures to follow, see Procedure 600 PR.1 Emergency Use of an Investigational New Drug (IND) or Device (IDE)).

600.6 Compassionate Use of an Investigational or Unapproved Device
For devices only, FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening condition (referred to as "compassionate use"). In these circumstances, FDA uses its regulatory discretion in determining whether such use of an investigational device should occur. Unlike emergency use of an unapproved device, prior FDA approval IS needed before compassionate use occurs. In order to obtain FDA approval, the sponsor should submit an IDE supplement requesting approval for a protocol deviation under section 812.35(a) in order to treat the patient. (See Procedure 600 PR.2 Compassionate Use of an Investigational or Unapproved Device.)

600.7 Use of Biologic in Research
Both the FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) have regulatory responsibility for therapeutic biological products, including premarket review and oversight. The categories of therapeutic biological products regulated by CDER (under the FDC Act and/or the PHS Act, as appropriate) are the following

- Monoclonal antibodies for in vivo use.
- Most proteins intended for therapeutic use, including cytokines (e.g., interferon), enzymes (e.g. thrombolytics), and other novel proteins, except for those that are specifically assigned to the Center for Biologics Evaluation and Research (CBER) (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, humans, or microorganisms, and recombinant versions of these products. Exceptions to this rule are coagulation factors (both recombinant and human-plasma derived).
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or down-regulating a pre-existing, pathological immune response).
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo.

Note: Please refer to the Transfer of Therapeutic Biological Products to the Center for Drug Evaluation and Research for updates that further define the categories of biological products that are regulated by CDER and CBER.

Related Information
IRB Policy 100: IRB Review of Research Proposals
IRB Policy 200: Informed Consent for Research Involving Human Participants
Yale University Policy on the Use of Controlled Substances in Research: http://www.yale.edu/ehs/consub.htm#
Connecticut Mental Health Center Department of Pharmacy Policy and Procedure Manual: Drug Distribution and Control, Section C-IX
Yale-New Haven Hospital Department of Pharmacy Services Investigational Drug Service Policy
Yale-New Haven Hospital Operating Room New Technology Committee
600 PR 1: Expanded Access/Emergency Use of an Investigational New Drug (IND) or Device (IDE)
600 PR 2: Compassionate Use of an Investigational or Unapproved Device
600 GD 1: Guidance on Data and Document Use for the IND Sponsor Investigator
620 FR 3: Application for Expanded Access Programs (EAP’s)
620 FR 2: Informed Consent Document for [Emergency or Expanded Access] Use Investigational Drug or Device
Contacts

<table>
<thead>
<tr>
<th>Subject</th>
<th>Contact</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational New Drugs or Devices</td>
<td>Human Investigation Committee</td>
<td>203-785-4688</td>
</tr>
</tbody>
</table>

Roles and Responsibilities

Human Investigation Committee

The HIC I, HIC II, HIC III and HIC IV serve as the four Institutional Review Boards or IRBs for biomedical human subjects research conducted by Yale University.

References

FDA Device Advice: Investigational Device Exemption (IDE)

FDA IRB Information Sheets – Medical Devices (Updated 9/98) http://www.fda.gov/oc/ohrt/irbs/devices.html#emergency

FDA Guidelines on Expanded Access Programs
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?CFRPart=312&showFR=1&subpartNode=21:5.0.1.1.3.9

Revision History: