A WIRB-Copernicus Group Company

A Guide for Researchers

Version 4.22
December 10, 2015

FS 616381

Western Institutional Review Board®
1019 39th Avenue SE suite 120 | Puyallup, WA 98374-2115
Office: (360) 252-2500 | **Fax**: (360) 252-2498 | **www.wirb.com**

The purpose of this guide is to provide you with information about WIRB's processes and clinical research issues. WIRB will from time to time amend or update the guide. WIRB will strive to keep the guide current, but cannot warrant its accuracy. The material provided is intended for informational purposes only, and should not be used as a substitute for legal and/or regulatory advice or opinions. For questions regarding legal interpretation, contact an attorney admitted to the bar in your state.

Table of Contents

1. Introduction

Western Institutional Review Board (WIRB) is pleased to provide this handbook of information about using WIRB as your IRB. The information is intended to provide practical guidance about submission questions, IRB review and oversight, and other topics that may be of interest to you and your research staff. Please use the information in any way that will serve to assist your research efforts as we join together in protection of the human research subject.

2. History of WIRB

Western Institutional Review Board (WIRB) was established in 1968 to provide human subject protection for endocrinology research conducted by Dr. Angela Bowen. The Board later reviewed a variety of research for other investigators in the local community, and Dr. Bowen incorporated WIRB in 1977.

With the introduction of the research regulations in 1981 came an increased need for independent IRB review services. In response, WIRB established the current for-profit structure, enabling it to serve an expanded clientele throughout the local community and across the United States.

WIRB first offered institutional IRB services in 1996. With the changing regulatory environment of the late nineties, WIRB extended its institutional services to several large university IRBs and other local IRBs. WIRB provides services to a growing number of institutions, while continuing to serve independent researchers around the world.

Over the years, WIRB has added services to meet researcher and subject needs. Subjects who call WIRB are able to reach a live operator any time of the day, any day of the week.

The Applied Research Ethics National Association established the Council for Certification of IRB Professionals (CCIP) in 1999 to advance the quality of human subject protection programs through a voluntary certification program initiated in 2000. A WIRB staff member was part of the first group to be recognized by CCIP as Certified IRB Professional (CIP), and more than 50 WIRB employees have since been certified.

In late 2001, WIRB implemented an electronic document storage system to provide the Board and staff with easy access to IRB records. In early 2003, after several years of development, WIRB implemented a validated electronic workflow and database system, allowing the staff to provide a higher level of support to the Board.

In 2003, WIRB was the first independent IRB to be accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In 2006, 2009 and

again in 2014, AAHRPP renewed WIRB's accreditation status. WIRB continues to be fully accredited.

WIRB strives to respond to the evolving needs of the global research community and has provided services internationally since 1986.

In 2001, in response to Canada's revised research review requirements, WIRB established a panel to review research conducted in Canada. The Panel, composed primarily of Canadian nationals, held its first review meeting in October 2001.

Today WIRB provides review services for more than 400 organizations (academic centers, hospitals, networks and in-house biotech research), as well as for individual investigators in all 50 states and internationally. WIRB has worked with all major pharmaceutical and device manufacturers, CROs, and the biotech industry. In 2007, WIRB started a panel devoted to dedicated clinical pharmacology units (such as phase 1 units).

In 2007, WIRB launched a web portal that allows WIRB's clients to track their submissions, view the review history and download regulatory documents. In 2009, WIRB began to offer "smart" online versions of many WIRB submission forms.

In 2012, Arsenal Capital Partners acquired WIRB and the Copernicus Group IRB and formed The WIRB Copernicus Group (WCG). Arsenal Capital Partners is a leading New York-based private equity firm that invests in middle market healthcare, specialty industrial, and financial services companies. In 2013, The WIRB-Copernicus Group acquired Research Dataware, LLC, software developer and provider of IRBNet, the leading software application supporting institutional review boards (IRBs).

WIRB's position within The WIRB-Copernicus Group provides it access to nationally recognized experts and processes. WIRB continues to operate independently, but benefits from the support and resources of The WIRB-Copernicus Group, the world's largest provider of regulatory and ethical review services for human research. We also enjoy a strong relationship with our sister companies, Copernicus Group IRB (CGIRB), Midlands IRB, Aspire IRB, New England IRB, and IRBNet, and through those relationships, we will leverage every opportunity to bring added value to you.

Effective December 21, 2015, new smart forms are available on the WIRB website. The new forms have been adopted by both WIRB and CGIRB and can be submitted to either IRB.

3. Regulations Affecting Clinical Research, Including HIPAA

A. The Regulatory Framework Within Which WIRB Functions

WIRB is registered with FDA/OHRP. WIRB's IRB registration number is IRB00000533, and WIRB's parent organization number is IORG0000432.

WIRB reviews many types of human subject research, including clinical research, behavioral research, and epidemiological research, in the United States and internationally. WIRB reviews research in accordance with three primary standards, as well as other regulatory standards, when appropriate:

- the Food and Drug Administration (FDA) Regulations on research with human beings (21 CFR 50 and 56), and
- the Health and Human Services (HHS) Regulations on research with human beings (45 CFR 46 Subparts A, B, C, and D),
- the International Conference on Harmonization (ICH) "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guideline."

The FDA regulations apply to clinical investigations conducted on medical products under FDA jurisdiction that will be marketed in the United States; principally drugs, devices and biologics.

The HHS regulations apply to research that is funded by HHS and other agencies that have adopted "the Common Rule," represented at 45 CFR 46, Subpart A. Institutions that receive federal funding for research must obtain an "assurance," a formal agreement with the government in which the institution promises to take prescribed steps for the protection of human subjects. Usually, the type of assurance will be a Federalwide Assurance (FWA) from the Office for Human Research Protections (OHRP). However, for some research, other types of assurances may be used or necessary. If you have questions about obtaining an assurance, see the section of this investigator handbook entitled "Special Considerations for Federally Funded Research," consult the OHRP web site, or contact WIRB's Client Services at 1-800-562-4789 or clientservices@wirb.com.

The International Conference on Harmonization (ICH) is an international standard for drug approval that has been adopted as either law or guidance in many countries (EU, Canada, Japan and the United States). In the United States, FDA has adopted it as guidance. ICH is similar to the FDA drug and IRB regulations, but has a few stricter standards.

WIRB has established written procedures that ensure that research approved by WIRB meets these three primary standards. However, WIRB may vary from the requirements of one of the three standards when it is not applicable. For instance, we will allow the investigator to vary from the ICH requirement that the subject receive a signed consent form for an HHS-regulated behavioral interview study conducted in a setting where a

signed copy of the consent form represents an unacceptable risk of breach of confidentiality for the subject.

In addition, WIRB reviews research funded by the Department of Defense, the Department of Education and other federal agencies.

B. HIPAA

WIRB also provides services under the Privacy Rule (45 CFR Parts 160 and 164 of the Health Insurance Portability and Accountability Act of 1996). WIRB will review requests for waivers of authorization and partial waivers of authorization for covered entities upon request (WIRB forms for requesting review of partial and full waivers of authorization are available on the Download Forms page of www.wirb.com as stand-alone documents and are also integrated into the Initial Review Smart Form available on the WIRB website December 21, 2015). WIRB will also review authorization language upon the request of a covered entity. If the authorization language is embedded in the research consent document, then the IRB must review it. If the authorization language is separate from the research consent document, then the covered entity may determine whether or not to submit the language for IRB review. WIRB will review separate authorization documents upon request.

4. Conflicts of Interest

WIRB considers that the most important step in managing potential conflicts of interest lies in appropriate disclosure, and this begins with the investigator's disclosure to a sponsor and the IRB of financial holdings, relationships, and other interests that might constitute a conflict of interest for the researcher as an investigator. When the researcher is a member of an institution, disclosure of potential conflicts to the appropriate institutional committee or office is also required.

In order to comply with the Department of Health and Human Services (HHS) guidance entitled "Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection," WIRB has established a policy for reviewing financial conflicts of interest of investigators, research staff and institutions. Please complete the designated Financial Interest Disclosure Form available on the Download Forms page of www.wirb.com.

The investigator or study staff will be considered to have a financial conflict of interest if the investigator, investigator's immediate family, the study staff, or the study staff's family

- Has a financial interest in the research with value that cannot be readily determined (for example, stock that is not publicly traded);

- Has a financial interest in the research with value that exceeds $5,000 other than payments for conducting the trial as outlined in the clinical trials agreement;
- Has a financial interest in the research with value that exceeds 5% ownership;
- Has received or will receive compensation with value that may be affected by the outcome of the study;
- Has a proprietary interest in the research, such as a patent, trademark, copyright, or licensing agreement;
- Has received or will receive payments other than payment for the conduct of clinical research from the sponsor that exceed $5,000 in the last 365 days;
- Is an employee of the agency or company sponsoring the research;
- Is on the board of directors of the sponsor;
- Has a financial interest that requires disclosure to the sponsor or funding source;
- Has any other financial interest that the investigator believes may interfere with his or her ability to protect subjects; or
- Is affiliated with an institution with a lower conflict of interest threshold than the amounts referenced above.

Diversified mutual funds or similar instruments in which the shareholder has no control over the equities held by the fund are not considered to present a conflict of interest.

With respect to rules issued by NIH (NOT-OD-11-109) **effective August 24, 2012, our reporting threshold for study teams was changed to $5,000**. [U.S. Department of Health and Human Services (HHS) issued a final rule (http://www.gpo.gov/fdsys/pkg/FR-2011-08-25/html/2011-21633.htm) in the Federal Register that amends the Public Health Service (PHS) regulations on Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought (42 C.F.R. Part 50, Subpart F) and Responsible Prospective Contractors (45 C.F.R. Part 94).]

WIRB also requires investigators and their research team to report planned recruitment bonuses. WIRB defines a recruitment bonus as an additional payment or incentive provided to the investigator or staff dependent solely on a particular number of subjects being enrolled, or dependent on the speed at which subjects are enrolled. The term "payment or incentive" includes any items of value, such as direct payment, gift certificates, travel vouchers, physical items such as watches, and so forth. Report such incentives in the Initial Review Smart Form available on the WIRB website December 21, 2015 or via the stand-alone recruitment bonus disclosure form available on the Download Forms page of www.wirb.com.

A financial conflict of interest is not intrinsically wrong. Rather, the purpose of analyzing a financial conflict of interest is to determine when the interest offers incentive to the investigators or other party to breach a duty to subjects or to society, and to determine how to address the conflict of interest. As individuals vary in their personal integrity,

and as the WIRB Board generally does not know investigators and other parties intimately enough to judge their integrity, WIRB uses two reasonable-person standards for analysis:

- First, the Board considers whether the financial conflict of interest could challenge the integrity of a reasonable individual.
- Second, the Board considers whether the financial conflict of interest would appear to a reasonable member of the general public to be a conflict that could challenge the integrity of the conflicted party.

Using these reasonable person standards, the Board considers the following factors in its analysis of the reported conflict of interest:

- Amount of Risk

The degree of risk and discomfort faced by subjects in research varies greatly. In high-risk studies, such as those involving the use of a medical device in invasive surgery, a conflict of interest could greatly affect the risks faced by subjects. In a study involving the analysis of human tissue, the risks to the subjects are generally limited to confidentiality issues.

- Effect of the Conflict of Interest on Subjective Decision-Making

The participation of the party with the conflict of interest could affect subjective decision-making, both consciously and subconsciously, and thus influence the conflicted party's judgment and behavior. Subjective decisions that could be influenced by a conflict include the design of the research, choosing which subjects to enroll, clinical care provided to the subjects, use of subjects' confidential medical information, data collection and analysis, adverse event reporting, and the presentation of research findings.

- Amount of Interaction Between the Conflicted Party and the Subjects

Many of the concerns about the conflicted party's decisions will be lessened if the conflicted party does not interact directly with subjects. For example, in many tissue studies the conflicted investigator simply receives waste samples from a surgery facility, and has no contact with the subjects. On the other hand, in a similar study the investigator may also perform the surgery, in which case the concerns over the effect of the conflict are greater.

- Other Parties Involved in Overseeing the Conflict of Interest

Often, there are other parties besides the IRB involved in the oversight of conflicts of research.

- Large institutions will often have a separate conflict of interest committee. (The standards for these committees are highly variable. WIRB has agreed not to

lessen the protections put in place by an institutional conflict of interest committee, but WIRB reserves the right to impose additional oversight.)
- For FDA-regulated studies, the FDA will be providing a scientific review of the research results.
- NIH does detailed reviews of research proposals in advance, and inquires about conflicts of interest at certain procedural steps.
- Some institutions have assigned subject advocates who sit in on the consent process.

The Board will consider the role and oversight of these and other such parties.

- Training in Conflict of Interest

The investigator or other conflicted party may have participated in training on the ethical analysis of conflict of interest and, therefore, may be more aware of the ethical issues and in need of less oversight.

- Nature of the Interest, and Relationship to the Research

The interest may be one in which large change is possible based on the outcomes of the study under review. An equity interest in a start-up company could be drastically affected by the research results, whereas stock in a large pharmaceutical company is not as likely to be affected. Is it a single site study or a multi-center study? The ability of the investigator or other conflicted party to affect the financial interest varies greatly in these different situations.

- Unique Investigator or Institution Qualifications to Conduct the Research

Occasionally, the investigator or institution is uniquely qualified to conduct the research. For instance, the investigational article may be a surgical device that has been developed by a surgeon who specializes in a surgical technique that only he/she conducts.

Possible Board Actions:
The following are actions the Board may take regarding conflicts of interest:
- A finding that the conflict of interest is not likely to jeopardize subject safety or bias the investigator's decision-making and does not require further action.
- A finding that disclosure of the conflict to subjects or others is necessary.
- A finding that controls on the conflict need to be put into place, such as limiting the role of the investigator with a conflict of interest.
- A finding that the conflict is unacceptable, and must be eliminated in order for the research to proceed.
- Other.

When a site submits an updated financial interest disclosure the Board will consider the new report and do the following:

- If the report is a document such as an annual update indicating no change to the previously reported financial interest disclosure, the report will be acknowledged.
- If the new disclosure is not significant enough to merit a change to the existing Board-directed management plan, the Board will approve and require no further action. This is a billable action.
- If the new disclosure merits an adjustment to the existing Board-directed management plan, the Board will direct appropriate changes to the management plan and approve the disclosure. This is a billable action.

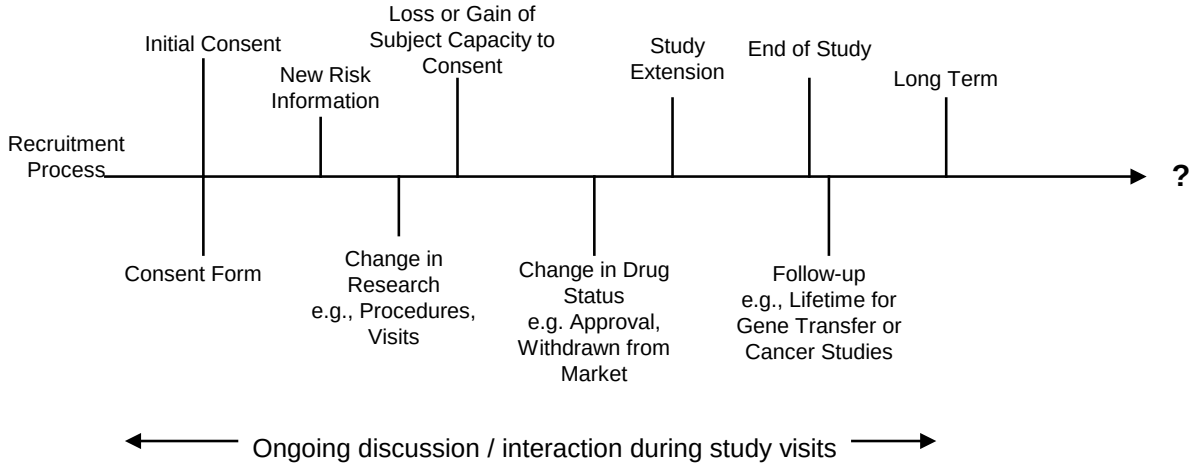
5. The Informed Consent Process

The informed consent process is central to the ethical conduct of research. It is an on-going conversation between the human research subject and the researchers that begins before consent is given and continues until the end of the subject's involvement in the research (see consent process diagram, below). There are various tools for the investigator to use to optimize this conversation, but the most important feature of informed consent is the investigator commitment to the process.

A. Goals of the informed consent process

- Give the subject **information** about the research
- Make sure the subject has **time** to consider all options
- Answer all of the subject's **questions** before the decision is made
- Make sure that all information is **understood** by the subject
- Obtain the subject's voluntary informed **consent** to participate
- **Continue to inform** the subject throughout the research study
- **Continue to re-affirm subject consent** to participate throughout the research study

B. Consent Process Diagram



C. Tools an investigator might use to assist the informed consent process

- Consent Form -- also called Informed Consent Form (ICF), Informed Consent Document (ICD) or Patient Consent Form (PCF)*
- Pamphlets or other reading materials*
- Internet information*
- Instruction sheets*
- Audio-visual presentations*
- Charts or diagrams*
- Discussions
- Consultation with others

**These items require IRB review before use.*

D. Investigator responsibilities in regard to informed consent

- Obtain consent before initiating study-specific procedures.
- Provide a **quiet, comfortable, and private setting** for the informed consent process whenever possible.
- **Explain** the consent process to the subject.
- Make sure the subject has **time to consider** all options; allow subject to take the form home before signing (whenever possible).
- Consider the **subject's reading abilities**. Check to make sure the protocol does not exclude subjects unable to read. If enrollment of limited or non-readers is allowed, involve an impartial witness in the informed consent process. WIRB has posted a standard generic form you can use to document the involvement of an impartial witness if your approved consent form lacks the necessary signature block for that; see the Download Forms page of www.wirb.com for the document titled "Impartial Witness form for Limited and Non-Readers."
- **Answer all questions.**
- To the extent possible, make sure the subject **understands enough information** about the research study to give informed consent.
- To the extent possible, make sure the subject can consent **free from coercion or other undue influence**.
- Since the informed consent process continues throughout the subject's participation in the study, c**onsent should be informally verified on a continuing basis.**
- **Significant new information** must be given to the subject, and continuing consent documented in some way; for example, new risk information presented to the subjected in an addendum to be signed by subjects who agree to continue to participate.

E. Issues to consider during the consent process

- Was the subject alert and, in your opinion, able to read and understand the language in the consent form?
- If the subject was unable to read the consent form, and limited or non-readers were allowed to participate, did you have an impartial witness present for the entire process? (An impartial witness is someone with adequate reading ability who is independent of the trial, who cannot be unfairly influenced by people involved in the trial, who attends the informed consent process while the consent form is being read to the subject, who reads the informed consent form and any other written information supplied to the subject, and who is willing to attest to this by signing the consent form.)
- If the subject is not fluent in English, was an approved translation of the consent form provided in the primary language of the subject? Was there also a bilingual translator present to assist with the informed consent process? Note: a translator alone is not considered adequate.
- Was the subject under any pressure (for example, family pressure, lack of medical insurance) to participate in the research? Was this discussed?
- Did the subject take time to carefully read the consent form, or read it along with you?
- Were the risks as set forth in the consent form carefully explained to the subject?
- Are there any other risks or concerns not stated in the consent form and were these explained to the subject?
- Was the subject asked if he or she had any questions about the study?
    - Did the subject have any questions or concerns?
    - Were the subject's questions answered?
    - Was the subject satisfied with the answer(s) they were provided?
- Did the person conducting the consent discussion check for subject understanding by asking some basic questions about the research? Did the responses reflect adequate understanding?
- Did the subject express a clear decision to proceed with the study?
- Was the consent form signed by the person who conducted the informed consent discussion?
- Was the consent form signed by a witness (if required)?
- Was the consent form signed by the Principal Investigator (if required)?
- If a Legally Authorized Representative is allowed to sign for the subject, were additional concerns about the subject's understanding and assent considered and addressed?

F. Consent by Legally Authorized Representatives

The laws regulating who can consent for *adults* who lack the capacity to consent for themselves are defined at the state level and vary from state to state. Persons who can consent for adults who lack the capacity to personally provide informed consent are known as Legally Authorized Representatives (LARs). See 45 CFR 46.102(c) and 21

CFR 50.3(l). Such trials, unless an exception is justified, should be conducted in individuals having a disease or condition for which the investigational product is intended.

WIRB's initial review submission forms solicit information about plans for use of LARs from investigators who plan to enroll adults who lack the capacity to consent for themselves. Sites should be able to explain how they determine which individuals meet the criteria for being a Legally Authorized Representative (LAR) under their state/provincial and local law. WIRB can provide a copy of the relevant statutes for your state upon request; however, advice from your legal counsel is strongly recommended. Sites should also be able to explain the process they use for verifying that an individual is qualified to serve as an LAR.

If the site's state/provincial/local laws regarding Legally Authorized Representatives are difficult to interpret, the sites may provide the Board with a letter from legal counsel which includes a statement such as the following: "The individuals who are authorized under state law to consent on behalf of a prospective subject to that subject's participation in the procedures involved in this research protocol are _____."

G. Consent by Subjects Who Cannot Physically Sign the Consent Form (due to physical impairment)

WIRB does not require a Legally Authorized Representative to provide consent for subjects who are *cognitively capable* of consenting, but *physically* unable (for example, due to paralysis). In those cases, obtaining consent from the subject with the assistance of a witness is usually sufficient. WIRB can provide additional guidance for these situations upon request.

H. Waivers of Consent for ***non-FDA*** studies

If you are requesting a waiver of consent and the research is not an FDA regulated study, then criteria from 45 CFR 46.116(d) must be met:

1. The research involves no more than minimal risk to the subjects.
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver or alteration.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

WIRB applies this standard to all requests for waiver of consent for non-FDA regulated research.

If you are a covered entity under HIPAA, the necessary information is collected via our Initial Review Smart Form available on the WIRB website December 21, 2015 or can be provided via the stand-alone WIRB form "Request for Full Waiver of Authorization Under HIPAA" available on the Download Forms page of www.wirb.com.

I. Waivers of Consent for *FDA* studies

For FDA regulated studies, waiver of consent must meet requirements of either 21 CFR 50.23 (a) - (c) (waiver of consent for individual emergency use) or 21 CFR 50.24 (emergency research without consent), or FDA guidance issued 04-25-2006 for In Vitro Diagnostic Device Study Using Leftover Human Specimens That Are Not Individually Identifiable.

For individual emergency waivers of consent, prospective IRB approval is not always necessary if a patient's life can be saved. See the FAQ on www.wirb.com titled "What is the difference between "Emergency Use" and "Treatment Use," and how do I determine which situation I have?" for more information, or refer to 21 CFR 50.23 (a)-(c).

If you are a covered entity under HIPAA, the necessary information is collected via the Initial Review Smart Form available on the WIRB website December 21, 2015, or can be submitted via the stand-alone WIRB form "Request for Full Waiver of Authorization Under HIPAA" available on the Download Forms page of www.wirb.com.

J. Waiver of Documentation of Consent

A waiver of documentation of consent is a waiver of the requirement for a signature on a consent form. The regulations allow the Board to approve this type of waiver if:

- The research is of minimal risk and involves no procedures for which written consent is usually required; or
- The only record linking the subject and the research would be the consent document and the principal risk of the research is the risk of breach of confidentiality.

Subjects enrolling in a study under this type of waiver must be provided with the elements of consent required by the regulations and subjects must consent to participate.

The Board will need to review the information that is provided to subjects to obtain consent to ensure that the required elements of consent are included in the consent discussion. Investigators requesting a waiver of documentation of consent must submit a written statement or script of this information for the Board's review. A template "Information Sheet" is available on the Download Forms page of www.wirb.com.

If your organization must comply with the Federal Privacy Rule (HIPAA), and the research requires you to use or share identifiable health information, the Information Sheet described above includes the required elements of an authorization. However, you should also request a Waiver of Authorization so the Board can determine whether it can waive the requirement for a signature on the authorization for use and disclosure of Protected Health Information. The WIRB form "Request for Full Waiver of

Authorization Under HIPAA" is available as a stand-alone form on the Download Forms page of www.wirb.com. The form is also integrated into the Initial Review Smart Form available on the WIRB website December 21, 2015.

K. Assent

When a subject may not be able to legally consent to research participation, a Legally Authorized Representative provides the consent for the subject. However, WIRB usually also requires that subjects who are not able to consent for themselves assent to participation if possible. "Assent" means a subject's affirmative agreement to participate in research. An investigator should not interpret a subject's failure to object as "assent" unless the subject has also affirmatively agreed to be in the research.

Assent is usually required for research involving *underage subjects* and research involving *adults with diminished capacity*. Assessing an adult's capacity to consent may be somewhat difficult, depending on the subject's medical/mental condition and the requirements of the protocol. If the investigator anticipates that some subjects may be able to consent while others may not, the investigator should establish a process to assess capacity.

Whenever there is doubt about capacity, the subject is best protected by involving a Legally Authorized Representative who knows the subject and is willing and able to participate in the informed consent process with the potential subject.

Assent is not a legally binding action, but within research ethics it is used to signify the agreement of the potential subject to participate in the research. WIRB will usually indicate which subjects' assent must be obtained and the method by which assent is to be obtained. The usual direction is as follows:

- Assent is not required for subjects 6 years and younger
- Verbal assent is required for subjects ages 7 through 14 years using the assent section below and the information sheet for children.
- Verbal assent is required for subjects ages 15 through 17 years using the Assent section below and the information sheet for adolescents (the reference to "17 years old" is modified by the Board when the local age of majority is not 18).
- Adults, assent is required, when the adult is capable, using the assent section in the Consent form.

ASSENT SECTION:

Statement of person conducting assent discussion:

1. I have explained all aspects of the research to the subject to the best of his or her ability to understand.
2. I have answered all the questions of the subject relating to this research.
3. The subject agrees to be in the research.
4. I believe the subject's decision to enroll is voluntary.
5. The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

_____ _____

Signature of Person Conducting Assent Discussion — Date

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____ _____

Signature of Parent or Guardian — Date

These instructions are modified by the Board when needed, to reflect the Board's assessment of subject condition and the potential risks and benefits facing the subject.

In order to assent, a subject must have at least a basic understanding of what might be asked of them in the research and what might happen. The information sheet should present this in simple wording and format.

The additional challenges an investigator faces in the assent process depend on the level of understanding the subject may be able to achieve. This will vary with each individual potential subject. An investigator may be able to obtain information about the subject's ability to understand from the person providing consent.

Recognition of the potential for unintended "coercion or undue influence" or "intimidation" is essential for the assent process. The person obtaining assent must take extra care to minimize these aspects of the communication between subject and researcher. At times this may mean having a different individual conduct the assent process in order to optimize the communication.

WIRB initial review submission forms ask sites if they plan to enroll **wards of the state**. Federal regulation 45 CFR §46.409 outlines special requirements for the involvement of wards in research. Sites that plan to enroll wards may be required to provide a plan for

appointing an advocate for each subject. Some state and local laws also further restrict enrollment of wards in research.

L. The Consent Form

The primary informed consent tool that involves both the researcher and the IRB is the consent form. This document is used in all research for which there is no approved waiver of consent. Thus, most research will involve use of an IRB-approved consent form.

An approved consent form must comply with several regulatory requirements:

- The required elements (as defined by the regulations) must be appropriately included.
- The content of the consent form must be understandable to a non-scientist.
- No waiver of rights or other exculpatory wording may be present or appear to be present in the consent form.

Satisfying the above requirements presents a joint challenge to the IRB and the investigator. In order to obtain WIRB approval of a consent form, the investigator may opt to do one, or a combination, of the following:

- Submit a *sponsor template* consent form for review (for multi-center studies, the sponsor template has often already been submitted to WIRB and reviewed)
- Submit an *investigator-written* consent form for review
- Request WIRB write the consent form

i. Some general guidelines for writing a consent form

Consent templates and/or outlines are available from WIRB, as well as from some NIH groups such as NCI, and other sources. *See Appendix 1 for a sample Consent Template.* Consent templates provide a framework and structure upon which to build a consent form.

- Consent forms should be written in simple, non-technical language for readers of a seventh-grade reading level who may not have taken science courses in school.
- Use the term “subject” rather than “patient” (the term “participant” may be used in some behavioral research).
- Avoid statements that suggest any waiver of subject rights or release from liability of the investigator or sponsor.
- Avoid use of “I understand” or “you understand” language as this may imply a level of understanding that is not present, and may discourage questions,
- Write all of the consent form except the consent section in the second person (“you are asked to”) rather than first person or third person.
- The consent section should be written in first person (“I consent to…”).
- Avoid wording that is, or may seem to be, coercive or overly reassuring to a potential subject.

- Do not make claims of safety or efficacy for investigational articles or procedures.
- Try to avoid the use of the terms “treatment,” “therapy,” or “therapeutic” (because these words may imply effectiveness).

ii. Consent form elements

The following is a list of the usual elements of a consent form *(including elements required by 21 CFR § 50.25; 45 CFR § 46.116; E 6 GCP 4.8.10).*

Introductory Information and Purpose

- Explain the research study and the expected duration of subject participation, and include the approximate number of subjects involved in the study.
- Reassure readers that it is appropriate to ask questions, and that they may take the form home for consideration (if appropriate for the given research).
- State clearly that the study is research.
- State the status of the test article based on the country where the research is being conducted; for example, in the U.S., drugs are “*approved*,” vaccines are “*licensed*,” and devices are “*cleared”* or *“approved for marketing*,” otherwise they should be designated as “investigational.”
- State the purpose(s) of the research; for example, drug protocols usually test for safety, tolerability and effectiveness.
- State why the person is being asked to participate in the study; for example, “You are being asked to participate in this study because you have been diagnosed with…”

Description of Study/Procedures

- Describe the visits and procedures (in agreement with the protocol), indicating which procedures are experimental.
- Briefly describe the study’s design; for example, “This is a dose escalation study. As subjects participating in the study tolerate a specific dose level, the new subjects entering the study will be given a higher dose of the study drug.”
- Explain the method used for determining if subjects will receive study drug or placebo, the method for assigning them to a group, and explain the chance of assignment to each group in the study.
- State the number of visits.
- Explain the length of study participation.
- Explain what happens at the visits. It is not necessary to list the procedures visit-by-visit, as detailed descriptions can result in an unnecessarily long consent form.
- Outline any additional participation requirements such as contraception requirements or prohibited activities.

Risks and Discomforts

- Describe any reasonably foreseeable risks and discomforts to the subject. Risks and discomforts must be stated in non-technical, layperson’s language.

- Provide the risks related to all drugs required by the protocol, including rescue medications, over-the-counter analgesics, and approved control group drugs.
- Include the possibility of allergic reactions and that serious allergic reactions can be life-threatening.
- Describe the risks and discomforts of invasive or unusual procedures, including protocol- required biopsies.
- Describe the risks and discomforts of blood draws, if subjects will have blood drawn.
- Include a statement explaining that there may be risks of participation and side effects which are still unknown.
- Whether known or unknown, explain the risks to women who are pregnant or who become pregnant during the study.
- Include a statement that unknown risks and discomforts are possible; if appropriate, include unknown risks to an embryo or fetus if a subject (or a subject's partner) is or becomes pregnant.
- Where applicable, include the risk that the subject's condition may worsen while they are in the study (whether assigned to active drug or placebo).
- If the study drug will be taken home and there is no childproof packaging or warning labeling, include a warning to keep it out of reach of children or others who may not be able to read or understand the label.

Expected Benefits

- Describe any possible benefits to the subject or others; indicate that benefits are not guaranteed.
- If statements regarding direct benefits of participation are included, they should be qualified as "possible" or that they "may" occur.
- Receipt of procedures and study items may be listed as benefits to the subject, but not in conjunction with their being "free" or at "reduced cost," as these statements imply a form of payment and thus should not be categorized as "benefits." The FDA Information Sheet "Guidance for Institutional Review Boards and Clinical Investigators" (1998) states, "Payment to research subjects for participation in studies is not considered a benefit, it is a recruitment incentive." Forms of payment may be referenced elsewhere, but not listed as a benefit of participation.

Alternatives

- Describe appropriate alternative treatments or procedures, if available.
- List several alternatives to participation if they exist; alternatives may include alternative drugs or therapy, palliative care, hospice care, etc.
- The consent form may say, "Your study doctor will discuss these with you."
- The section on alternatives should include a brief summary of the risks and benefits of the alternatives.

Costs

- Describe any known or anticipated costs to the subject.

- State who is responsible for the costs of the study-related items such as medications, procedures, device, visits, hospitalization and treatment for possible side effects.
- Indicate which procedures and items will be provided at no charge.
- If insurance will be billed for anything, include information about possible costs to the subject or their insurance. If anything is being billed to insurance, discuss what happens if the insurance does not pay.

Payment for Participation

- Describe the planned prorated payment for participation, if any.
- Any money or other incentive of monetary value should be listed in this section rather than the benefit section.
- If subjects are to be paid, state specifically for which visits subjects will receive payment and when such payment will be made; for example, "payment will be made at the end of each study visit," "payment will be made at the end of the last study visit" or "payment will be made within one month after the last study visit." Be as specific as possible to minimize confusion. Consider whether any aspects of the total amount or the proration plan may be coercive or unduly persuasive (WIRB does not routinely allow more than half the total payment to be assigned to the last visit). The Board may require revision of the payment or payment schedule.

HIPAA Authorization or Confidentiality:

Describe the limits on confidentiality of information in this section.

Prior to HIPAA, the section on confidentiality was often titled "Confidentiality," but is now usually titled "Authorization To Use And Disclose Information For Research Purposes" and includes more information for the subject as outlined by the HIPAA regulations. Some sites (such as, those outside the U.S.) are not bound by the Privacy Rule and may opt to include only the confidentiality information required by the sponsor, 21 CFR 50 and 56 and/or 45 CFR 46. Some covered entities also opt to use a stand-alone authorization and exclude authorization language from their consent forms. Please indicate in your submission whether your site will need to have a HIPAA authorization section in the consent form (or whether you will use your own separate authorization form or are not a covered entity).

The authorization section presents the information required by the federal regulations regarding patient privacy rights. WIRB has developed standard template wording for the authorization section that identifies the parties who can use and disclose the PHI as well as the parties to whom the PHI may be disclosed. It also includes the following required information:

- A meaningful description of the PHI, which can be edited for each study.
- A description of each purpose for the use and disclosure.
- Information about the subject's rights related to the authorization.

- Information about the expiration of the authorization (some states such as California, Delaware, Illinois, Indiana, Washington, and Wisconsin have state laws that require an expiration date).
- Instructions on how to revoke the authorization.
- A statement about what may happen if the authorization is not signed.
- A warning that once information has been released, it may no longer be covered by the Privacy Rule and may be released again without further authorization.

WIRB also ensures that the authorization section is modified as needed based upon local law; for example, authorizations for California sites are placed at the end of the consent form with their own signature lines and in 14 point font.

Compensation for Injury

- Outline the plans for compensation and/or medical treatment for research-related injury or illness, including who will be responsible for the costs.
- Explain what will happen if the subject gets injured. Explain how they will get treatment.
- Clearly state who will pay for treatment if the subject is harmed.
- Address what will happen if the subject's insurance is billed for the treatment, but refuses to pay.

WIRB requires that the clinical trials agreement (CTA) between the sponsor and the investigator (or investigator's institution) and the approved consent form do not conflict with each other regarding the compensation for injury. For example, if your CTA indicates that expenses for treatment of research related injury will be paid, the consent form must state this as well. Before submitting a request for review of a new research project to WIRB, please consider what method you will use to ensure that no subjects are enrolled unless the CTA and the WIRB-approved consent form are in agreement. WIRB accepts a variety of plans, for example:

- The research is minimal risk research for which compensation for injury language in the consent form is not necessary.
- There is no CTA for the research.
- The research is funded by a government agency (such as NIH) that does not offer compensation for injury.
- Upon receipt of WIRB approval documents, the investigator will check the CTA against the WIRB-approved consent form and resolve any conflicts via a request for a consent form modification to WIRB and/or a modified CTA before enrolling subjects.
- The sponsor or CRO may agree to review the WIRB-approved consent document and resolve any conflicts via a request for a consent form modification to WIRB and/or a modified CTA before authorizing enrollment at this site. **WIRB requires the name and signature of the sponsor or CRO representative, or written correspondence from the sponsor or CRO indicating who will take this responsibility.**

- The PI's hospital, university or medical center has a contract with WIRB for IRB services, and it has an established process for ensuring that the compensation for injury language in the CTA and in the consent form do not conflict.
- The PI's hospital, university or medical center has an established process for ensuring that the compensation for injury language in the CTA and in the consent form do not conflict. (Submitters must provide a description of the process.)
- Sites may also submit plans that differ from any of the plans outlined above.

Questions

Regulations require that a contact be provided for each of the following types of questions.

- Questions about the research.
- Questions about research-related injury or illness (the Board prefers a physician be listed as the contact for injury or illness) or study problems.
- Questions about their rights as research subjects (list WIRB and, if desired, a local or institution IRB contact).

Voluntary Participation/Withdrawal

- State that the subject's participation is voluntary and that a subject may withdraw at any time for any reason.
- State that the subject's decision not to participate or to withdraw from the research early will involve no penalty or loss of benefits to which the subject is otherwise entitled.
- State that the subject's participation may be ended by the study doctor or sponsor at any time for any reason without the subject's consent. Include any specific reasons cited in the protocol. General reasons may also be included. *Please note:* the FDA may stop the research, but will not stop the participation of an individual subject.
- Include information on any risks involved with withdrawing early; for example, the need to taper the study drug, obtain follow-up, be placed on standard medication, etc.
- Indicate that subjects who withdraw after the start of the study may be asked to return for a final visit and final study procedures, and must return the study drug.

Trial Registration

A new rule for informed consent was announced in the Federal Register: January 4, 2011 (Volume 76, Number 2) Page 256-270. The compliance date was March 7, 2012 for clinical trials that are initiated on or after the compliance date. As of that date, the following statement must be included in consent forms for "applicable clinical trials" as defined in FDAAA, 42 U.S.C. 282(j)(1)(A), section 402(j)(1)(A) of the PHS Act, and any relevant regulation.

> *"A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."*

Since this wording is only required for certain types of clinical trials, and only for those initiated on or after the compliance date, WIRB does not automatically include the text in all existing and new consent forms. Individuals that wish to have the text in their consent forms should request it. Our initial review submission form solicits information about whether the research will be posted to clinicaltrials.gov.

Other

- Explain that significant new information that may be related to the subject's willingness to remain in the research will be provided to the subject.
- Identify the source of funding for the research.
- Disclose conflicts of interest (financial and otherwise).
- State that the subject will receive a copy of the signed and dated consent form.

Consent

This section changes to first person for emphasis; for example, "I voluntarily agree…" or "I have..."

- Include a statement of the subject's consent to participate, as well as an authorization to release medical (or research, as appropriate) records to the parties in the HIPAA authorization (or confidentiality) section, if applicable; and a statement that the subject is not giving up any legal rights by signing the consent form.
- Include a statement that the subject has read the information in the consent form or had it read to her/him (as appropriate); however, don't include statements which imply a level of comprehension, such as "I understand…"
- Include a statement that the subject's questions have been answered.

Signatures and Dates

- Include appropriate signature and date lines for consent as applicable.
- Include a space for the person conducting the informed consent discussion to sign (required by ICH).
- Provide a line for the investigator to sign if desired by researcher or sponsor; however, this is not a WIRB requirement.

iii. Assent Forms

When an adult subject is not able to legally consent to participate in the research, a Legally Authorized Representative (LAR) provides the consent for the subject. For children, parents or guardians provide consent for minor children. However, WIRB usually also requires that both incapable adults and children assent to participation if possible.

Assent requires that subjects have at least a basic understanding of what might be asked of them, and what might happen. WIRB recommends providing a simple assent information sheet that explains the research to older children and adolescents.

Template Assent Information Sheets for Children and for Adolescents are included in Appendix 2 and Appendix 3, respectively.

iv. Improving the Readability of a Consent Form or Assent Information Sheet

- Decrease sentence length.
- Limit each sentence to one thought or topic. Avoid run-on sentences.
- Use simpler words; for example, select words with fewer syllables.
- Use common words. Remove technical jargon and medical terms.
- In discussing risks, use the symptoms the subject might experience rather than just the medical terms for the problem.
- Use short, simple paragraphs.
- Use correct basic grammar and form.

When evaluating a proposed word or phrase, consider whether a reader with no college education, no science courses, and little or no exposure to the medical professions would easily understand it. Most words or concepts can be explained in simple language.

When drafting a consent form, frequently ask "Does the reader need this information in order to make an informed decision?" Avoid including excess technical information that would only confuse or intimidate a reader.

v. Special Considerations for Gene Transfer (Gene Therapy) Consent Forms

The following is based on Appendix M (NIH Guidelines for Research Involving Recombinant DNA Molecules, April 2011).

Word Choice in Gene Transfer Consent Forms:
Use the term "gene *transfer***"** instead of "gene *therapy*." Replacing the term "therapy" with "transfer," helps diminish any implication of effectiveness.

Use a neutral term such as "product," "vaccine," or "agent" instead of "drug" or "medicine" to refer to the investigational gene transfer product. The goal would be to help assure that subjects understand they are receiving recombinant DNA that may act differently than many conventional drugs.

Try to avoid the use of the terms "treatment," "therapy," or "therapeutic" (because these words may imply effectiveness that has not been proven). The following are some suggested techniques for avoiding extensive use of the term "treatment":

- Substitute the word "dosing," or "group" for "treatment":
  - "If you are assigned to ~~Treatment~~ group A, …"
  - "At the end of the ~~treatment~~ dosing phase, …"
  - "~~Treatment~~ Dosing in the study will stop …"
- Delete the word "treatment":
  - "Subjects may receive up to 12 cycles ~~of treatment~~ if there is ..."
- Substitute the name of the agent:
  - "If you receive ~~treatment with~~ ABC 123."

- "…effects of ~~your treatment~~ABC 123 and/or chemotherapy on …"

- Address the increased possibility of **loss of confidentiality** because of media and public focus on the research.
  ***Example*:** Research studies involving gene transfer have received a great deal of attention from the media. Although every effort will be made to protect your identity and that of your family, this attention may result in a greater risk than usual that information concerning your study participation will appear publicly without your consent.

Additional Consent Form Elements for Gene Transfer Consents:

- Inform subjects that an **autopsy will be requested if the subject dies**.
  ***Example*:** In the event of your death, an autopsy will be requested. It would be done to provide additional information about the research. Your family and your "legally authorized representatives" have the right to refuse the autopsy even if you sign this consent form.

Additional Risk Information Considerations for Gene Transfer Consents:
Consider the special characteristics of the gene and vector involved and discuss common and/or unknown risks:

- Where will the agent end up in the body?
- How long will the agent be in the body?
- Can it be transmitted to others (*horizontal transmission* to those in contact with the subject, or *vertical transmission,* to offspring via egg or sperm)?
- Is there a risk of leukemia (with retroviral type gene transfer vectors) or other types of cancers or conditions (for example with angiogenesis-type agents)?
- Are there special precautions which must be taken because of these risks?

M. Review of "e-consent" (electronic consent) forms

Electronic consent ("e-consent") via web applications and/or electronic tablets such as an iPad is growing in popularity. WIRB is a leader in this area. WIRB reviews e-consent technologies during development and in their final form to ensure that they meet the regulatory requirements for the elements and documentation of consent. This section provides some simple best practices on how to prepare an informed consent IRB submission so that it is suitable for use in an electronic consent tool.

i. e-consent submission timing
   Sponsors and investigators considering eConsent may wish to obtain IRB approval of the consent document **text** prior to developing the electronic consent tool. Revisions based on IRB feedback are easier to implement before e-consent programming and animation has begun.

ii. e-consent submission items
   For a typical e-consent IRB submission, the Sponsor and e-consent vendor will jointly prepare the IRB submission of materials. Typical submissions include:

a. scripts for any video or audio files
b. storyboards for any planned video creation
c. content for any screens on the e-consent tool that will be viewed by the patient

iii. Conditional and final approval

The IRB's decision to conditionally approve versus defer will depend on the extent to which the draft version reflects the content of the final electronic version. If the bulk of the electronic process has been provided in draft text or in story boards, then the IRB can conditionally approve the consent form. However, if there is still substantial content to be developed, then the IRB must defer the consent form for future board review. Sponsors must determine how much time and resources they want to commit to developing an electronic consent before seeking an IRB decision.

The most optimal process is for the sponsor to provide in writing to the IRB a complete description of the electronic consent process, with story boards for videos if applicable. Then the IRB will likely be able to provide conditional approval and have a single individual review the final product.

If the final step is solely the transfer of the IRB approved consent form to the tablet, without any modification of the text wording, the IRB does not have to conditionally approve the consent form and does not have to review the final version of the consent form on the tablet. The IRB can issue a final approval of the consent form. If there are photos or audio materials to add to the final version, then the IRB should review the final electronic version.

N. Description of WIRB's Preferred Vendor for e-Consent

In 2013, WCG partnered with Mytrus, Inc., a pioneer in "virtual clinical trials" and technologies that improve clinical trial efficiency, to deliver a unique electronic informed consent solution that will help to streamline and enrich the clinical research process.

Mytrus' technology solution brings unmatched insight and integrity to the consent process, ensuring that patients are properly informed and enabling sponsors to obtain meaningful data regarding patient consent and trial enrollment.

"Enroll" is the Mytrus innovative, patient-friendly electronic informed consent and patient enrollment system for clinical trials. Mytrus is pioneering patient-centered technologies that enable people to participate in clinical trials in a better-informed and more convenient way. Enroll has been independently proven to improve a patient's

understanding of research studies and is currently being used by leaders in the pharmaceutical community to Reinvent Consent™.

- The tool is meant to assist a patient in making an informed decision when consenting to a study
- Speaks to a general level of the informed consent process overall and emphasizes the rights and responsibilities of the patient
- Narration and visual cues promotes patient engagement and involvement in the consenting process which helps to make the study information more comprehensible, and makes it easier to process the information of the study
- The tool is not intended to replace the interaction/communication between the consenter and consentee, rather it is designed to enhance the consenting process

Benefits to trial participants who are consented using the Mytrus iPad e-consent technology:

- Better understanding of risks and benefits
- Improved learning through animation and visual imagery
- Tool promotes dialog
- Clear and easy study explanation
- One-Stop (i.e., HIPAA, Bill of Rights, Genomics, etc.)

Benefits to Sponsors whose sites use the Mytrus iPad e-consent technology:

- Improved compliance and oversight
- Greater transparency into clinical site and CRO
- More informed study participants
- Evaluated comprehension
- Real time visibility to screening and enrollment activity

Working with WIRB and Mytrus:

- The Mytrus enroll™ system works best with sites that can use the sponsor template consent form without substantial alteration. It can easily accommodate your site's compensation for injury text and payment for participation plans, but additional signature lines, blanks for subjects to initial each page and so forth are customizations that cannot be easily incorporated into the interactive tool that all sites share.

How does it work?

- The Mytrus enroll™ system is validated for compliance with 21 CFR § 11 and ICH/GCP, which supports assurance of security and privacy of information managed by the system.
- Each person who will have access to the iPad will have a unique username and pin code that should not be shared.
- No electronic data is permanently stored locally at the site(s) by the Mytrus solution.

- All data that is sent to the iPad server, is encrypted at the time that it is sent.
- Electronic records and signatures have audit trails, as required by 21 CFR § 11 and ICH/GCP and all data in the database is audit trailed in compliance with FDA and ICH guidelines.
- All data provided through the sponsor web portal is de-identified data.
- During Study Close Out, Mytrus works with the Sponsor to provide de-identified data for the study on media as agreed upon by the sponsor policies. Participant data is archived by Mytrus and maintained as per sponsor terms and policies.
- As there is no data stored on the iPad, nothing can be retrieved if an iPad is lost or stolen. However, Mytrus maintains a mobile device management account on each iPad for the length of the study which allows us to push current content to the iPad, locate a lost or stolen iPad, and wipe all applications from the iPad remotely if necessary.
- Data stored on the Mytrus secure server is in a third party hosting environment which is SAS 70 (type II)/SSAE 16 certified facility and is HIPAA compliant.
- Direct data access is restricted to identified Mytrus IT staff who are trained to handle PHI and PII. Log-monitoring and intrusion detection system (IDS) appliances as well as firewalls are installed on our production network.
- All data on the server receives daily incremental backups and weekly full backups that are maintained in redundant hosted environments via private network in separate geographical locations. Mytrus uses a secure private cloud server system through Rackspace with data hosted under Safe Harbor Certification.

O. Certificates of Confidentiality

For some types of research, the Board may direct an investigator to obtain a certificate of confidentiality. A Certificate of Confidentiality helps researchers protect the privacy of human research participants enrolled in biomedical, behavioral, clinical and other forms of sensitive research. Certificates protect against compulsory legal demands, such as court orders and subpoenas, for identifying information or identifying characteristics of a research participant.

Investigators might consider applying for a certificate for research involving subject populations peculiarly prone to face legal or social harm by another's discovery of their private, confidential, or protected information that can be exploited legally. For example, research that involves subjects involved in illegal, stigmatized, or embarrassing behavior; subjects with illegal status (alien, child runaway, AWOL, etc.); and subjects with a stigmatized disease (HIV, alcoholism, mental illness, etc.) might have additional protection if a certificate of confidentiality has been obtained.

Frequently asked questions about certificates of confidentiality are available on the NIH web site here: http://grants.nih.gov/grants/policy/coc/faqs.htm and OHRP has posted guidance here: http://www.hhs.gov/ohrp/policy/certconf.html. Instructions for applying for a certificate are available here http://grants.nih.gov/grants/policy/coc/appl_extramural.htm, but NIH is not the only source for one, as several federal agencies issue certificates.

The Department of Justice requires that researchers prepare a "Privacy Certificate" (PC), which is similar to a Certificate of Confidentiality (CoC) for all research it regulates. This requirement applies to the Department's research arm, the National Institute of Justice (NIJ) and its other parts, such as BJA, OJJDP, OJP, etc. More information is available here: http://www.ojp.gov/nij/funding/humansubjects/confidentiality.htm.

P. Pregnant Partner Consent

Many protocols now include instructions for investigators to collect data on the outcome of pregnancies that occur in partners of male subjects. WIRB follows 45 CFR 46, which defines research as use of private, identifiable information for research purposes. Since investigators would be obtaining private information from the pregnant partner and infant, the partner would be a subject in the research. Investigators must obtain consent from the pregnant partner before any data collection can occur, and WIRB requires a consent form to be submitted for these subjects if a pregnancy occurs.

If plans for obtaining consent from the pregnant partner (or a request for a consent waiver) are not submitted at initial review, the Board may approve the research, but place a note like the following on the Certificate of Approval "The Board noted the protocol references pregnancy in partners of male subjects. The Board would like to emphasize that if you interact directly with the pregnant partner or obtain identifiable private information about the pregnant partner, the partner is a subject in this research. You must obtain consent with a WIRB-approved consent form from the pregnant partner before any data collection can occur. If WIRB has not approved a pregnant partner consent form for this protocol, WIRB has a template consent that we can provide to you for this purpose. Please contact us if you have any questions."

A sample information release form template for obtaining consent from partners who become pregnant and for collecting data about their infants is available in Appendix 4 of this document and on the Download Forms page of www.wirb.com. The template form cannot be used without WIRB approval.

6. Working With WIRB for IRB Review – An Overview

Western Institutional Review Board is composed of several individual review panels. Panels meet twice a week [except for WIRB's Canadian panel and the Executive Policy Committee]. Institutional IRBs formed under the Powered by WIRB program meet less frequently.

If not eligible for expedited review, new protocols are assigned to panels based on both the specialty required to review the protocol and on the next available panel meeting. The upper right corner of the WIRB Certificate of Approval displays the panel assignment.

Reviews for investigators at Canadian locations are assigned to the WIRB Canadian panel; therefore, a protocol taking place in both the United States and Canada will be assigned to both a U.S. panel and the Canadian panel.

WIRB conducts expedited review of certain kinds of research involving no more than minimal risk to human subjects and one or more procedures listed in the categories published in the Federal Register. In minimal risk research, the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Users who create a Connexus account can access detailed tracking information and can download review documents from the site. Click on "LOGIN TO CONNEXUS" link on the home screen of www.wirb.com to set up an account.

To learn more about accessing research review details on WIRB's web site, WIRB's panel structure, or to determine the panel assignment of a particular protocol, call Client Services at (360) 252-2500 or e-mail clientservices@wirb.com.

The protection of confidential business information and trade secrets is vital to the interests and the success of WIRB. All the employees and Board members are required to sign confidentiality agreements as a condition of employment, and WIRB follows industry standards on the protection of electronic data in our Part 11 compliant system.

Confidential Disclosure Agreements (CDAs) between sponsors and Western Institutional Review Board (WIRB) are not required by WIRB. However, we are happy to enter into a CDA if preferred by the sponsor. If you require a Confidentiality Agreement, your request will be directed to WIRB's General Counsel for preparation.

7. Submitting Documents for WIRB Review

A "smart" online form is available for most WIRB submissions (such as initial review and changes in research). The "smart form" submission is generally a shorter process because it dynamically omits questions that are not relevant, based on the answers you provide about the research. Click "LOGIN TO CONNEXUS" on the www.wirb.com home page to set up an account.

Users who complete their submission online receive an e-mailed confirmation that WIRB has received the submission. It includes a reference number that will facilitate discussions of the submission with WIRB staff. The confirmation e-mail also serves as an official WIRB acknowledgement of receipt. Documents submitted via Connexus are also stored there for other users with access to your workspace to view.

8. Materials required for initial review

The following is a general list of items required by WIRB to begin the review process for a research study.

A. Items required for all initial review requests

Materials marked with an asterisk may be omitted if WIRB is already in receipt of a current version. This may include a WIRB-approved consent form for a previously approved protocol, as well as recruitment and other subject materials.

- **WIRB Submission Form** For best results, WIRB recommends use of its smart submission forms, (for international research, a smart version is not yet available)
  - For investigators conducting research outside of the United States and Canada, WIRB provides an **international version of its submission form.**
- **Protocol***
- **Current professional license** for Principal Investigator, showing the expiration date*
  (Federal Regulations do not recognize Co-Principal Investigators; therefore, if two PIs plan to share oversight of a single study, the Board requires a completed submission form for each investigator and holds each individually responsible for the conduct of the entire study. Canadian regulations do not allow for approval of Co-Principal Investigators of any kind.)
- **Curriculum Vitae (CV)** for Principal Investigator and each Sub-Investigator*
- **Consent form*** (If WIRB has not already approved one). . Please submit consent forms as Microsoft Word compatible files (.doc, .docx, .rtf).
- **Other materials to be provided to the subjects** which are not included in the protocol, such as advertisements, questionnaires, subject diaries, etc.*
  (Any commercially available validated instruments cited in the protocol that are used without modification are not listed individually on the Certificate of Approval; however, approval of the protocol does extend to the uses of such industry standard forms as described in the approved protocol.)

i. For drugs, biologics and food supplements

Provide a copy of each of the following:

- **Investigator's Drug Brochure***
- **Background Information for Food Supplements***
- **Canadian Qualified Investigator Undertaking Form** (Canadian sites)
- **Health Canada No Objection Letter (NOL) if available** (Canadian sites)
- **Documentation from sponsor or FDA verifying the IND (Investigational New Drug) number if one is required for the research.* If an IND is not required, provide the reason why in writing.**

- **For gene transfer studies subject to RAC review, please submit the RAC correspondence, Appendix M responses, and Institutional Biosafety Committee (IBC) approval and minutes (if available). If the IBC review has yet to occur, please provide a date for the intended review and contact information for your NIH-OBA registered IBC. WIRB can provide IBC oversight; see the Review Services tab at www.wirb.com.**

ii. If a DEVICE study, provide device manual (also called "Instructions for Use") and ONE of the following:

- **Unredacted FDA Letter** granting the Investigational Device Exemption (IDE);* OR
- **Letter from sponsor** stating that the study is a non-significant risk device study and the basis for that determination;* (**unredacted**) OR
- **Documentation of why the investigation is exempt** from the IDE requirements under 21 CFR § 812.2(c) (such as the PMA approval letter/number or 510(k) clearance letter/number) or otherwise exempt.*****

Physicians seeking approval to use a Humanitarian Use Device (HUD) on-label, may use the WIRB initial review submission form designed for such review requests -- The WIRB HUD On-Label Use Submission Form is available on the Download Forms page of www.wirb.com – please note that on December 21, 2015, that form will be retired and physicians should instead use the Initial Review Smart Form available on the WIRB website. (See the FDA guidance titled "Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and Food and Drug Administration Staff Humanitarian Device Exemption (HDE) Regulation: Questions and Answers" for more information about requirements for use of HUDs.)

B. Suggested Guidelines for Writing a Research Protocol

If you will be drafting a protocol for submission to WIRB, the following guidelines will help you to include the necessary elements.

i. Cover Sheet

- Display protocol title, protocol identifying number, and date. Amendments should be numbered and dated.
- Display the name and address of both the sponsor and the medical monitor (if someone other than the sponsor).
- Display the name and title of the investigator responsible for conducting the research, and the address and telephone number(s) of the research site(s).

ii. Purpose of the study and background

- **Purpose of the study:** State the specific scientific objective(s) (aims) of the research.

- **Background:** Provide background material which supports the purpose of the research, and which is detailed enough to allow someone who is not an expert in the field to understand the context of the question, and the study design. References may be cited in the Background section.

iii. Criteria For Subject Selection

- **Number of subjects:** State the total number of subjects expected to participate. For multi-center protocols, this should include both the overall total and the number of subjects to be enrolled at each site.
- **Gender of Subjects.** Describe the intended gender distribution of the subjects. If there are any gender-based enrollment restrictions, explain the nature of the restriction(s) and provide justification. Equitable inclusion of both men and women in research is important to ensure that both receive a proportionate share of the benefits of research and that neither bears a disproportionate burden. Therefore, subjects of both genders should be included in the research unless there are appropriate medical or scientific reasons for excluding them. Women of childbearing potential may not be routinely excluded from participating in research; however, pregnant women should be excluded unless there is clear justification why they should be included. A clear statement whether pregnant women are included or excluded is also required, along with the justification.
- **Age of Subjects.** State the age range of the subjects. Provide the rationale for selecting this age range. Participation of adult subjects in research should not be age-restricted unless there is scientific or medical justification. Check the age of majority in the jurisdiction where the study is to be conducted and whether special considerations apply to research with minors. Additional restrictions may apply to research involving minors.
- **Racial and Ethnic Origin.** Describe the intended racial and ethnic distribution of the subjects. If there are any enrollment restrictions based upon race or ethnic origin, explain the nature of the restrictions and provide justification. Within the limitations imposed by the population of the study site(s), research should include sufficient enrollment of persons of diverse racial/ethnic backgrounds to ensure that the benefits and burdens of research participation are distributed in an equitable manner.
- **Inclusion Criteria.** List the inclusion criteria. These should be based on the scientific rationale and safety considerations, and should define who will be eligible as a subject.
- **Exclusion Criteria.** List the exclusion criteria. These should be scientifically valid and help further define the subject population. Subjects at particular risk from the study interventions or procedures should be excluded. Be sure to account for warnings, precautions, and contraindications listed in current product labeling.
- **Vulnerable Subjects.** If vulnerable subjects (such as, those with limited autonomy or those in subordinate hierarchical positions) are included, justify their inclusion. Children, pregnant women, nursing home residents

or other institutionalized persons, students, employees, fetuses, prisoners, and persons with decisional incapacity are examples of vulnerable subjects who may be in need of greater protection. Additional restrictions or requirements may apply to research involving vulnerable subjects.

iv. Methods and Procedures

- **Methods and Procedures.** Summarize the research design and sequentially identify all procedures to be used to accomplish the specific aims of the project. Clearly identify and distinguish procedures that are considered experimental, procedures that are performed exclusively for research purposes (including "extra" routine tests), and procedures that would occur regardless of the research (i.e., standard of care). Point out any procedures, situations, or materials that may be hazardous, and the precautions to be exercised to maintain subject safety.
- **Data Analysis and Data Monitoring.** Describe the statistical or analytical methods to be used. For all studies involving greater than minimal risk, describe how the data will be monitored to ensure the safety of the subjects. For research involving intervention that entails potential serious risk to subjects, compares blinded treatments over a long time period, or which may call for "stopping rules" for certain endpoints, a data monitoring committee may be required to protect the safety or welfare of subjects. A detailed description of its operation (such as, membership, function, frequency of review, stopping rules) should be included.
- **Data Storage and Confidentiality.** Describe where the research data will be stored during and after the study and how it will be secured. The investigator must take necessary steps to maintain confidentiality of data. This includes coding data and choosing an appropriate and secure data storage mechanism preventing unauthorized access to data. State who will have access to the data and how the data will be used. If data with subject identifiers will be released, specify the person(s) or agency to whom the information will be released and the purpose of the release (such as, routine verification of case report forms).
- **Transition from Research Participation.** If applicable, describe how subjects terminating their participation in the research will be returned to their usual care (such as, taper study medication and resume usual medication, return to primary care provider).

v. Risk/Benefit Assessment

(a determination as to the risks and benefits of the research to subjects is the responsibility of the IRB; however, the following information is still required in the submitted protocol)

- **Risk Category.** State the risk that the research presents as one of the following: Minimal, or Greater than Minimal. Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations

or tests. A risk is a potential harm associated with the research that a reasonable person would likely consider injurious. The definition of minimal risk for research involving prisoners is somewhat different: the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

- **Potential Risk.** Describe the potential risks associated with the study. Risks are not only physical, but can be psychological, sociological, economic, or legal. Risks include any specific toxicities noted in the investigator's brochure. If possible, estimate the probability that a given harm may occur and state its potential reversibility.
- **Protection Against Risks.** Describe how the study design will prevent or minimize any potential risks or discomfort. Potential risks and discomforts must be minimized to the greatest extent possible such as by subject monitoring, appropriate subject withdrawal criteria and follow-up.
- **Potential Benefits to the Subjects.** Describe potential medical benefit(s), if any, for subjects participating in the research. If there are no anticipated benefits, this should be stated.
- **Alternatives to Participation.** This section should include a description of alternative therapies or courses of action which are available should the subject elect not to participate in the study.

vi. Subject Identification, Recruitment And Consent/Assent

- **Method of Subject Identification and Recruitment.** Describe how prospective subjects will be identified and recruited. The identification and recruitment of subjects must protect privacy and be free of undue influence. Recruitment of an investigator's own students, employees and patients is considered coercive in most circumstances. The steps taken to minimize undue influence must be included if these individuals are to be enrolled as subjects.
- **Process of Consent.** Describe or list everyone who is authorized to obtain consent and how the process of informed consent will be structured to be conducive to rational and thoughtful decision making by the subject (or subject's legally authorized representative) without any element of coercion or undue influence. If used, 'Auditor/Witness' roles would be described in this section.
- **Subject Capacity.** If not all subjects will have the capacity to give informed consent, describe how capacity will be assessed and by whom. Describe the anticipated degree of impairment relative to their ability to consent to participate in research. Research with persons who have diminished capacity is allowed only for minimal risk trials; therapeutic benefit trials; and non-therapeutic trials where the objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally, the foreseeable risks to the subjects are low, the negative impact on the subject's well-being is minimized and low, the trial is not prohibited by law, and the approval of the IRB is expressly sought

on the inclusion of such subjects, and the IRB written approval covers this aspect (ICH 4.8.14).
Note: Occasionally a site may have enrolled a subject in a trial where loss of capacity was not contemplated (such as an oncology trial), but would like to keep a subject who unexpectedly lost capacity enrolled and make arrangements for consent by a legally authorized represent; please request WIRB review of these situations as a change in research.

- **Subject/Representative Comprehension.** All investigators have a legal and ethical obligation to ensure that prospective subjects or subjects' representatives have sufficient knowledge and comprehension of the information represented by the elements of informed consent to enable them to make an informed and enlightened decision whether or not to participate or allow participation in research. In this section, describe how it will be determined that the subject or subject's authorized representative understood the information presented. This section should clearly document that the investigator has an adequate plan in place to assure an acceptable level of comprehension before consent is obtained. If children or decisionally impaired adults will be subjects, this section should also include a specific plan to assess comprehension during assent (the subject's agreement).
- **Debriefing Procedures.** In psychological studies where any information will be purposely withheld from the subject, state the information to be withheld, justify this non-disclosure, and describe the post-study debriefing of the subject.
- **Consent Forms.** Consult IRB consent form guidelines for specific sections required for consent documents. [See 21 CFR 50.25 available on the FDA website, or the FDA guidance at http://www.fda.gov/oc/ohrt/irbs/informedconsent.html]
- **Documentation of Consent.** The PI is responsible for ensuring that valid consent is obtained and documented for all subjects. If not already addressed above (see Process of Consent section), specifically describe how consent will be documented and how and where documentation will be stored.
- **Costs to the Subject.** Describe and justify any costs that the subject will incur as a result of participating in the study. This section should clarify who (such as, sponsor, grant, subject) will pay for procedures associated with the study or necessary follow-up. Normally, subjects should not have to pay for research procedures that do not provide direct benefit. No charge may be made to subjects for costs covered by another entity. Subjects may not be charged for investigational drugs without the written permission of the FDA.
- **Payment for Participation.** Describe any reimbursements or payments (such as, cash, coupons or gift certificates, academic credit) that the subjects will receive for participation. List the prerequisite condition(s) that must be fulfilled by subjects to receive these payments. The amount must be justified and not constitute undue inducement of the subject to

participate in the research or to continue beyond where they would have otherwise withdrawn. To protect the subject's right to withdraw without penalty, the IRB requires a prorated system for financial payments. In most circumstances, no more than 50% of the total payment may be withheld till the end of the study. Payments should accrue as the study progresses and subjects do not have to complete the entire study to be eligible to receive a payment.

C. Requirements for Human Subject Protection Training

WIRB requires investigators to verify on the initial review submission form and each Continuing Review Report form that each member of the research team has successfully completed training in human research subject protection. *Your institution may have additional training requirements, please check with your institutional official.* Please note that HIPAA training or prior research experience alone does not satisfy this requirement for training in human subject protection. WIRB's expectation is that training include topics such as ethical principles related to human subject protections, federal regulations for protection of human subjects, and Good Clinical Practice. Canadian sites are strongly encouraged to complete the Tri Council Policy Statement online training. If your team has not completed TCPS training, please be sure an equivalent training has been completed and is listed in the submission.

When standard therapy is part of the research, WIRB only requires human research subject protection training of staff members who are involved in the consent process, recording of data, submission of unanticipated problem reports or other procedures specific to the research.

WIRB accepts training completed in a variety of formats (such as online modules, live seminars, college courses, self-study texts that provide CEU or CME credit) and from a variety of sources (such as government entities, non-profit institutions, professional organizations, and commercial businesses). .

Examples of courses are listed below. You are not limited to these training resources. Additional opportunities are available through other sources. External links are provided for user convenience and do not represent an endorsement by WIRB.

Online:

- Courses available through WCG Academy. (The WIRB-Copernicus Group® (WCG) has partnered with UL EduNeering® (UL), the foremost provider of cloud computing learning solutions, to create WCG Academy™, an FDA-adopted, Part 11-compliant training program for clinical research professionals. Designed by experts in clinical research and adult learning, the WCG Academy curriculum is interactive and role-based, helping adults to retain more information than any other learning solution. WCG Academy also provides robust dashboards and metrics to foster compliance and efficiency.)

- WIRB is a participating organization in the Collaborative Institutional Training Initiative (CITI). Investigators submitting research to WIRB can meet the training requirement through CITI or CITI International. CITI training for U.S. research is available at: https://www.citiprogram.org. CITI International training for non-U.S. or international research is available at: www.citiprogram.org. (The international course is available in English, Spanish, and Chinese. Additional languages may be available in the future.)
- The NIH Office of Extramural Research provides an online tutorial called "Protecting Human Research Participants" http://phrp.nihtraining.com/users/login.php.
- Canadian researchers may obtain training through the Tri-Council Policy Statement (TCPS). Training is available in English http://www.pre.ethics.gc.ca/eng/education/tutorial-didacticiel/ . If your team has not completed TCPS training, please be sure an equivalent training has been completed and is listed in the submission

Self-study text offering CME credits:

- Protecting Study Volunteers in Research - A Manual for Investigative Sites by Drs. Dunn and Chadwick (ISBN 1-930624-44-1). The book can be purchased through the publisher, Thomson-Centerwatch.

Physicians and their teams who request approval of on-label use of a humanitarian use device or single patient treatment use of an investigational product are not required to complete human subject protection training.

D. Suggested Guidelines for Evaluating Staff Levels at the Site

WIRB's **initial review submission forms** ask for information about staffing levels at the site. WIRB evaluates site staffing levels based on a variety of criteria.

At a minimum, all clinical sites should have the following:

- Enough trained investigators and staff to administer the protocol without deviations that impact subject safety or data integrity.
- Enough trained investigators and staff to ensure there is sufficient time available for staff to interact with the subjects as much as is necessary for good clinical care.
- Enough trained investigators and staff to provide coverage for emergencies.

In addition, the Board considers what level of staffing would be required to execute the protocol. For example:

- How many subjects are already enrolled and what is the predicted rate of accrual?
- How many visits are required by the protocol?
- What type of visits are required and will the subject need to see the investigator at each visit?
- Are the required procedures complex or lengthy?

- Does the administration of the study drug require supervision or extensive instruction?
- Are the subjects generally healthy, seriously ill, or suffering from multiple conditions?
- Is the disease involved acute or unpredictable?
- Are the side effects of the intervention expected to be numerous or serious?
- Are the subjects considered vulnerable?

The particular composition and expertise of the study staff also is a consideration:

- Does the investigator have experience in conducting research? (This variable can affect overall management of the research staff and functions.)
- Are the staff members experienced in conducting research? Are they skilled at maintaining accurate and complete study records?
- Do the investigator and staff have experience with the type of treatment in the protocol?
- Does the site have other ongoing protocols?

For example, the Board might determine that an experienced research coordinator can administer 3 to 5 drug protocols that require weekly or biweekly visits of ½ hour to 2 hours and enrollment of 5 to 15 subjects. However, if the site's ratio amounted to 7-10 of these studies per experienced coordinator, the Board might defer the research and ask for more information about the staffing levels. The Board would also expect to see at least one physician sub-investigator appointed to provide back-up for the PI.

Different types of protocols, however, require different levels of staff time and expertise. Because of their narrow inclusion criteria, oncology protocols normally don't rapidly accrue subjects, and because they are often carried out by groups of oncology specialists, the Board might tolerate a high protocol-to-staff ratio. In these cases, the Board's focus might shift from the number of staff, to the ability of a large staff to successfully coordinate a subject's care and execute the study plan.

In the case of a non-treatment protocol, the question of staff levels may not be important.

E. Compensation to Investigators for the Conduct of Research

Financial compensation to investigators should be at fair market value for the procedures and services provided. WIRB will review "bonus payments" and other compensation to investigators that is not directly tied to payment for study procedures or services on a case-by-case basis. (AMA Code of Medical Ethics Policy #E-8.0315)

F. Special considerations for Drug Research: Do you need an IND?

WIRB's **initial review submission forms** ask for information about an IND. As a general rule, WIRB requires that a sponsor or investigator obtain an IND from FDA for clinical investigations involving drugs or dietary supplements. However, if the

investigation uses a marketed drug, the sponsor or investigator may propose that the investigation is exempt from an IND under 21 CFR § 312.2(b), which states:

> (b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
>
> (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 the 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 the 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 set forth in part 50; and
>
> (v) The investigation is conducted in compliance with the requirements of Sec. 312.7 [regarding marketing and promotion].

Criteria (i), (ii), and (v) are under the control of the investigator and/or sponsor, and WIRB holds the investigator and/or sponsor responsible for complying with those criteria. Criterion (iv) is satisfied by the fact that the study has been reviewed by WIRB.

WIRB will consider whether the conditions for (iii) are met, and send a letter to the sponsor addressing that item.

For clinical investigations using a dietary supplement, WIRB will require that the sponsor or investigator obtain an IND if the protocol is designed to provide information on a health claim. However, WIRB will accept a written statement from FDA that an IND is not necessary for a given clinical investigation of a dietary supplement.

G. Special considerations for Device Research

The FDA regulations establish additional requirements on the part of the IRB for the review of studies using medical devices. Before reviewing research involving a device (or devices), the Board must identify and evaluate the regulatory status of the device(s) (such as determining whether the device study qualifies as a Non-Significant Risk (NSR) Device study, a Significant Risk (SR) Device study, or whether the research use of the device is exempt from the IDE regulations).

If you believe the device is NSR and the Board agrees, then the Board may go on to review the research. However, if the Board disagrees, and finds the study to be SR,

and there is no IDE assigned, it will provide the investigator and, if appropriate, the sponsor, with its finding. The sponsor is responsible for notifying the FDA of the Board's SR determination. The Board will not review the research until the sponsor provides written proof that either the FDA has granted an IDE to the sponsor or that the FDA disagrees with the Board's SR determination and has determined that the device is NSR. If the FDA has not responded to the IDE application, as described in FDA 21 CFR § 812.30, this proof may consist of a letter showing that an IDE application was submitted at least 30 days prior to the date on which the submission was forwarded to WIRB.

If the research is SR, provide WIRB with proof of the IDE number at the time of submission. The Board will automatically consider the research to be SR. In most cases, submitters should ensure WIRB receives a copy of the IDE letter that has not been redacted. Redacted IDE letters generally do not provide sufficient information for the Board.

If the subject must undergo a medical procedure as a part of the study, and that medical procedure is not one which the subject would otherwise undergo as part of standard medical care, the Board must consider the risks associated with the procedure as well as the use of the device. If potential harm to subjects could be life-threatening, could result in permanent impairment of body function, or permanent damage to body structure, the device should be considered SR.

If approved devices will be used as part of the research, each site may be asked to confirm that the device(s) they are using are being used within their approved labeling.

H. Special considerations for Behavioral Research

WIRB reviews behavioral research. Behavioral research is non-clinical research, and oftentimes is qualitative rather than quantitative. When submitting behavioral research, provide a detailed protocol, a description of the protections of confidentiality that will be used, and a description of the consent process. Also, if deception is involved, the submission must also include a description of the information to be withheld, a justification for the non-disclosure, a description of potential psychological or other risks to subjects resulting from the deception, and the process for post-study disclosure of the deception and debriefing of the subjects, including provisions for psychological counseling or other follow-up which may be needed.

I. Special considerations for Federally Funded Research

i. Grants

For federally funded research, WIRB must review a complete copy of the grant application. There is an exception to this requirement for multi-site research; the requirement for IRB review of the grant applies only to the awardee institution. The grant generally need not be reviewed by the IRBs (including WIRB) at non-awardee institutions participating in the multi-site research; however, there may be situations or

certain types of research in which the Board may require the complete grant as part of its review for an investigator at a non-awardee institution.

ii. FWAs

When an institution (a legal entity) receives federal funding for research, the institution usually must obtain an assurance as required under section 45 CFR § 46.103 of the Common Rule. Each separate legal entity that is engaged in the research must obtain an assurance. For research funded by agencies that are part of the Department of Health and Human Services (HHS), this will usually be a Federalwide Assurance (FWA) obtained from the Office for Human Research Protections (OHRP. Those agencies outside of HHS that have adopted the Common Rule may accept a Federalwide assurance, or may use a different assurance mechanism. OHRP provides guidance on when an institution is engaged in research at http://www.hhs.gov/ohrp/policy/engage08.html.

Prior to the Board's review of federally funded research, the following requirements must be met:

1) As described in the OHRP guidance entitled "Engagement of Institutions in Research," a Federalwide Assurance (FWA) must be filed for all sites engaged in federally-funded research. The guidance is available at http://www.hhs.gov/ohrp/policy/engage08.html . OHRP requires all FWA applications be submitted electronically using the electronic submission system available through the OHRP website at http://ohrp.cit.nih.gov/efile/, unless an institution lacks the ability to do so electronically. If an institution believes it lacks the ability to submit its FWA electronically, it must contact OHRP by telephone or e-mail (see http://www.hhs.gov/ohrp/assurances/contact/index.html) and explain why it was unable to submit its FWA electronically. The registration number for WIRB is IRB00000533. WIRB will request a copy of the DHHS-approved FWA application, but if it is not available, it is not required for review.

2) An IRB Authorization Agreement must be completed. See appendix 5 for a sample pre-filled authorization agreement in which WIRB is listed as Institution A. Complete the Institution B sections of the form. The form is also available on the Download Forms page of www.wirb.com.

Additional information about FWAs and IRB review of federally funded research can be found on the OHRP website at http://www.hhs.gov/ohrp/.

Contact WIRB's Client Services for clarification or assistance regarding these requirements.

J. Special considerations for multi-center studies

Each individual submission for a multi-center study must be accompanied by a completed WIRB initial review submission form. We recommend using the "smart"

form available from the Download Forms page of www.wirb.com. The "smart form" submission is generally a shorter process because it dynamically omits questions that are not relevant, based on the answers you provide about the research.

For investigators conducting research outside of the United States and Canada, WIRB provides an **international version of its submission form.**

Any site submission lacking a complete submission form, current CV and license, or proof of a current medical license (when applicable) may not be scheduled for review until the missing information is submitted. Depending on the type of research, additional information may also be required. Contact WIRB Client Services for information about submission requirements for specific types of research.

The sponsor or CRO contact will receive copies of the reviewed documents sent to investigators, unless otherwise requested in writing.

i. Consent forms for multi-center research

Once the Board has reviewed and approved a consent form for a multi-center protocol, WIRB will provide an approved version of that form, unless the submitter provide alternate instructions. **Reliance on the previously-approved version can significantly reduce the processing time, and result in more rapid receipt of approval documents**. WIRB will generate a consent form for the PI by incorporating any institutionally-required language that has been provided to WIRB and the site-specific information such as payment information, etc. into the previously-approved consent.

Site-specific information which must be provided on the WIRB submission form includes:

- All **telephone numbers** for the consent form, including a 24-hour number for emergencies (for research that is greater than minimal risk) .
- **Payment for participation** information. Indicate either "no payment" or provide a statement explaining the payment plan as you would like it to appear in the consent form (amounts, visits not paid, when payment will be made). Please double-check your math, and please submit to us the exact wording you would like to have used. Misunderstandings concerning the subject payment plan are a major source of corrections and subject complaints. Also, please be sure your payment plans agree with the sponsor's preferences, if any.

To determine if a previously approved consent form is available for a particular protocol or request to preview it, contact Client Services at 1-800-562-4789 or check the Connexus page for that protocol (your sponsor or CRO contact can grant you access).

More details about consent form review is available on the WIRB FAQ's page at www.wirb.com.

ii. Impact of changes

Investigators who provide instructions for use of an a consent form other than the one already approved by WIRB or who request significant changes to that version will experience delays in the review process while their unique consent forms are prepared for Board review. Additional delays may occur if the Board has questions about the consent form or if the investigator does not accept Board-required changes to the submitted consent form.

iii. National ad campaigns / Advertisements for all investigators

Sponsors and CROs will benefit from submitting **advertising and other recruitment materials** with the initial review submission, as later submissions incur a fee for review. Audio and video recordings must be accompanied by the script. Please submit the script for review before the advertisement is recorded, so that any board-directed changes can be reflected in the recording.

For best results, when submitting subject recruitment materials or other subject materials (diaries, questionnaires, etc.) that have been previously reviewed by WIRB, state in the submission that the items have been previously reviewed by WIRB. Board support staff will provide the Board with information about the previous Board review, so that the previous decision of the Board can be taken into account when the additional materials are reviewed.

iv. Pre-Review submissions

WIRB can assist sponsors and CROs during the planning stages of a multi-center study by pre-reviewing the protocol and subject materials, including a template consent form. The fee for initial review applies.

If the Board finds the research as reviewed acceptable, the submitter is issued a letter documenting the Board's determination, a redlined template consent form indicating the Board's changes, and appropriate documentation of the review of the other subject materials submitted. It is important to note, however, that no Certificate of Approval (COA) is issued, and the research cannot go forward until appropriate documentation for an investigator has been received and reviewed by the Board, and a COA has been issued for that investigator.

The following is a general list of items needed by WIRB to conduct a pre-review:

- Completed WIRB initial review submission form for pre-review (downloaded from the Download Forms page of www.wirb.com - "**Initial Review Submission Form for Sponsors and CROs**") and sent to WIRB. Please note that effective December 21, 2015, that form will be retired replaced with a general purpose Initial Review Smart Form available on the WIRB website.
- Protocol
- Template Consent form
- Other written materials to be provided to the subjects that are not included in the protocol, such as questionnaires, subject diaries, etc.

If a **drug/biologic** or food supplement study, provide a copy of the following:

- Investigator's Drug Brochure (may be omitted if WIRB is already in receipt of a current version)
- Background Information for Food Supplements
- Documentation from sponsor or FDA verifying the IND (Investigational New Drug) number if one is required for the research. If an IND is not required, provide the reason why in writing.

If a device study, provide device manual (also called "Instructions for Use") and ONE of the following:

- Unredacted FDA Letter granting the Investigational Device Exemption (IDE) for the proposed use; OR
- Letter from sponsor stating that the study is a non-significant risk device study and the reason for that determination (please do not provide a *redacted* copy); OR
- Documentation of why the investigation is exempt from the IDE requirements under 21 CFR 812.2(c) (such as the PMA approval letter/number or 510(k) clearance letter/number) or otherwise exempt.

Following Board review, individual investigators may be submitted.

- Sites that plan to use the pre-reviewed template language should not include a consent form document with their submitted review materials. WIRB will use the submission form information from each site to add site-specific information (such as telephone numbers, payment for participation, etc.) to the consent form template approved by the Board.

- When WIRB receives a submission from a site in Canada and the research was pre-reviewed by a U.S. panel, the submission is reviewed by WIRB's Canadian panel, which reviews and modifies consent forms according to Health Canada regulations. Language in consent forms approved by the Canadian panel may differ from the language in the template consent form produced by a WIRB U.S. panel.

  Sponsors of research involving multiple Canadian locations may benefit from requesting a pre-review by WIRB's Canadian panel prior to submitting Canadian investigators for review.

- When WIRB receives a submission from an investigator at an institution, WIRB may modify the language in the template consent form to conform to the institution's requirements.

If WIRB does not receive an investigator submission within 10 months of the original review, WIRB will inquire if the sponsor plans to submit any sites. If the sponsor indicates they plan to submit more sites, WIRB will keep the protocol open. If the sponsor indicates they do not plan to submit sites after all, or if WIRB does not receive a response to the

inquiry, the protocol will be closed (in the event that WIRB receives an investigator submission for the protocol, WIRB will schedule a new review of the research; initial review fees apply).

v. Single Review Solution™ (SRS)

WCG is the only ethical solutions provider –in the world– to offer a streamlined, unified Single Review Solution™ (SRS) for all sites involved in a clinical trial. Whether sites are private, central or institutionally based, each is reviewed under one Institutional Review Board (IRB) umbrella using WCG's proprietary SRS process. SRS leverages the members of the WCG family of companies – Western Institutional Review Board® (WIRB), Midlands Independent Review Board (Midlands IRB), Aspire Independent Review Board (Aspire IRB), New England Independent Review Board (New England IRB) and Copernicus Group Independent Review Board® (Copernicus IRB) – to deliver increased efficiency in its review of clinical trials.

SRS connects WCG's industry clients with over 1,000 academic medical centers, universities and hospitals for which WIRB is an IRB of record. Using Copernicus IRB's central site review processes, WCG provides a single, seamless review of the protocol and its associated sites. Among its many advantages, SRS allows our clients to work with a single IRB, and to manage the IRB review process and its related documentation in one place.

K. Special considerations for international research

i. Canadian researchers

The WIRB Canadian Panel is located in Vancouver, Canada. Its membership is compliant with the requirements outlined in the Division 5 regulations of Health Canada. The panel is able to review research for Canadian sites that do not need to use their own local research ethics board. For more information about the WIRB Canadian Panel, please call Client Services at 800-562-4789 or the WIRB Canadian office in Vancouver at 604-872-5030.

ii. Countries requiring dual IRB review

When WIRB reviews research in other countries, it obtains information on local laws and local attitudes, and welcomes the help of investigators and sponsors in obtaining this information. WIRB prefers that in international research there be a local IRB or other review committee that oversees the research in addition to WIRB, in order to help ensure that the research is culturally acceptable. However, WIRB is willing to consider international research in which there is no local IRB as long as dual IRB review is not required by local law and WIRB is able to receive adequate information about the cultural acceptability of the research.

iii. Consent form considerations for non-English speaking countries

When WIRB enters into a dual IRB agreement with another IRB to oversee the research, all changes to the consent form will be subject to approval by both IRBs. When the WIRB-approved consent form is translated by the other IRB, WIRB will not routinely conduct its own verification of the translation (as is customary for translations for studies conducted in the U.S. and Canada) unless the circumstances warrant it. Translated versions of the consent form are not required to display a WIRB approval stamp and sites are not required to adhere to the statement on the second page of the Certificate of Approval which says “Provide non-English speaking subjects with a certified translation of the approved consent form in the subject's first language. The translation must be approved by WIRB unless other arrangements have been made and approved by WIRB.”

If you will NOT be partnering with a local IRB who will oversee the translation(s), the translation must be approved by WIRB. If you produce your own translation, submit it for review along with a copy of the certificate from the translator attesting to the fact that the document(s) are true and accurate translations of the WIRB-approved consent form or other subject material.

L. Special considerations for investigators at institutions

In addition to meeting the requirements of WIRB, an investigator at an institution may be subject to local institutional requirements. Institutional investigators should check with their local research office to determine what requirements, if any, must be fulfilled prior to submitting research to WIRB. Such issues as pre-review by internal committees, use of template consent form language, and approval/submission through a central office should be addressed with your local institutional officials.

M. Special considerations for subjects who do not speak English

All consent forms and other subject materials must be in a language easily understood by the subject, and all translations must be approved by WIRB. WIRB provides translations services for WIRB-approved sites only.

If you are enrolling non-English speaking subjects, you must have plans for conducting the consent discussion in the language understandable to the subject, and for ongoing communication with the subject throughout the research and in case of emergency. The WIRB initial review submission form solicits information about plans for ensuring adequate communication. Sites may, for example, ensure at least one member of the research team is fluent in the language, and that research staff member(s) will be available during emergencies; or ensure the research team has 24-hour access to a translation service with sufficient medical expertise to discuss the research.

i. WIRB-Arranged Translations:

Translations requested on the submission form are sent to a qualified translator **after the English materials are finalized and sent to the site**. This timeline ensures the materials sent for translation are the final version.

If a research study is approved without a translated consent form and a non-English speaking subject later qualifies for enrollment, the site can obtain a translated version of the consent form for use in consenting the subject by submitting a request to WIRB. The request should identify the Sponsor, Sponsor Protocol Number, Investigator, and the language requested. The subject cannot be enrolled until they have received the WIRB-approved translated consent. If WIRB is asked to provide a price quote for the translation, the translation process will not begin until WIRB receives authorization to proceed.

WIRB bills an administrative fee for translation services in addition to the translator's fee. The bill is sent to the party requesting the translation or their designee (WIRB requires written confirmation that the designee will accept the invoice).

WIRB suggests that before sites request a translation, they check with their sponsor to determine if the sponsor already has made a translation or arrangements for translation, and if not, if the sponsor is willing to pay for a WIRB translation.

Starting in January 2016, WIRB will begin issuing approvals for translated documents. This harmonizes our processes with that of our partner IRB, CGIRB.

ii. Sponsor/CRO/Site Translations:

The WIRB-approved version of the consent form or other materials may be translated and submitted to the Board along with a certification statement signed by the translator that identifies the specific translated documents and attests to the translator's fluency and the accuracy of the translation from English to the target language (see sample format below). The translation must correspond to the WIRB approved version of the material; therefore, a translation of the sponsor template consent form or materials is not acceptable.

If the translation is acceptable, the approval date will be affixed by WIRB staff and an approved copy sent to the site.

Other documents (such as subject diaries, subject instructions) need to be legible (faxed copies often are not legible) and accompanied by a translator certification statement.

Sample Certification Statement:

CERTIFICATION

I hereby certify that I am fluent in English and [name of language] and that I have, to the best of my knowledge and belief, made a true and complete translation from English to [name of language] of the WIRB approved [name of document; such as, Research Subject Information and Consent Form, advertisement] for [sponsor / protocol number], [WIRB protocol number] this _____ day of _____, *[month / year]*.

_____
(Signature of Translator)

Name of Certification (*ATA, DSHS, other*)_____
Certificate No._____

iii. Unexpected Translations Needs:

WIRB has the following policy regarding the use a short form consent process to enroll subjects who do not speak English. This policy is limited to the situation when **both** of the following are true:

- A full-length version of the consent form in a language understandable to the subject is not available, and
- It is in the subject's best medical interest to be enrolled in the research before a translated consent form can be obtained.

The short form will follow the OHRP template short form[1], and the subject will have to be reconsented within 30 days with a WIRB-approved consent form in a language understandable to the subject. Several certified short form translations are posted and available for use on the www.wirb.com Download Forms page.

Each of the following steps must be followed:

1. The Principal Investigator is to insert study specific information, including title of study, principal investigator, and contact information into the OHRP template short form.
2. The subject must be given a copy of the short form in the language understandable to him/her to read;
3. A translator/interpreter must orally present the entire IRB-approved English ICF;

[1] Online at http://www.hhs.gov/ohrp/policy/ic-non-e.html#sample

4. The consent process must be witnessed by an individual who is fluent in both English and the subject's language;
5. The English ICF must be signed by the person obtaining consent as authorized under the protocol and the witness;
6. The short form must be signed by the subject and witness;
7. The subject must be given signed copies of the English ICF and short form;
8. The original signed English ICF and the original signed short form should be retained in the subject's research record and medical record, if appropriate; AND
9. The PI will then obtain a fully translated version of the consent form at the earliest opportunity. The subject would then be re-consented using the translated consent form within 30 days.

N. Special considerations for enrollment of wards of the state

WIRB initial review submission forms ask sites if they plan to enroll **wards of the state**. Federal regulation 45 CFR §46.409 outlines special requirements for the involvement of wards in research. Sites that plan to enroll wards may be required to provide a plan for appointing an advocate for each subject. Some state and local laws also further restrict enrollment of wards in research.

O. Special considerations for single-patient expanded access

i. Support of the WCG Foundation, Inc.:

The WCG Foundation is a 501(c)(3) public charity founded to strengthen protections for research participants and improve health and well-being worldwide. The Foundation raises and distributes funds for three program areas: supporting expanded access to experimental treatments (compassionate use) for desperately ill patients who have exhausted all other options, advancing education and training in research ethics, and providing scholarships for the WIRB International Fellows Program.

When appropriate - and with approval from FDA, the drug manufacturer and an IRB - these patients can gain access to experimental drugs and medical devices. Because insurance typically does not cover expenses associated
with approval process, many patients can't afford what they consider a last chance for hope. WCG Foundation seeks to reduce this financial burden by paying for IRB review of applications for single-patient expanded use.

WCG Foundation accepts contributions from individuals, institutions, other foundations, and private and public organizations. For more information about the Foundation or to make a gift, go to www.wcgfoundation.org.

ii. About single-patient expanded access:

In February 2015, the FDA published draft guidance "Individual Patient Expanded Access Applications: Form FDA 3926". The draft guidance introduces and describes

draft Form FDA 3926 (Individual Patient Expanded Access—Investigational New Drug Application (IND)).

iii. Special submission requirements:

In order to review a single-patient expanded access, please provide the following information:

- Completed WIRB Single Patient Expanded Access Submission Form
- Consent Form. **For your convenience, a single patient consent form template you can use to write your own and submit to WIRB for review is available from WIRB.**
- **Documentation of FDA IND** Number, if available
- **IB (or reference to existing information) or supporting literature**
- CV for the treating physician (if a current one is not already on file with WIRB)
- Medical License for the treating physician (showing the expiration date) (if a current one is not already on file with WIRB).

If you have any questions, or if we can be of further assistance, please contact us. If, after submitting the requested information, the patient's condition changes such that he/she no longer needs approval of the single patient expanded access request, please notify us at your earliest opportunity.

9. IRB Transfer

An IRB transfer happens when a study that has been approved by another IRB is transferred to WIRB. Transfers happen for a variety of reasons -- if an investigator decides to change IRBs for some reason, if a local IRB is closing, or if the study is at an institution that has recently signed a contract with WIRB.

A. Required documentation for an IRB transfer review request:

- WIRB Initial Review Submission Form
- Background information provided on the WIRB **"Cover Letter/Checklist for Transfer of IRB Oversight to WIRB"**
- A copy of the complete current protocol if not already on file at WIRB
- A copy of the currently approved consent form (the one approved by the previous IRB)
- Any documents that the submitter has been instructed to provide based on his/her answers to the questions on the **Cover Letter/Checklist for Transfer of IRB Oversight to WIRB** form (for example, the form instructs the submitter to provide any new risk or benefit information that was not submitted to the previous IRB).

B. Clinical trials undergoing IRB transfer fall into two categories:

1. **"Active"** – some or all subjects are on active* treatment and the site may recruit more subjects for the study.
2. **"Follow-up only" –** the site will not recruit any more subjects, but still has subjects in follow-up (subjects no longer on active* treatment).

*WIRB acknowledges that the definition of “active” may vary, depending on the type of research being transferred. For drug studies, generally if a subject is no longer receiving any study drugs (active drug, control, placebo, etc.), but the investigator is collecting follow-up data on them, then those subjects are in follow-up, not “active.”

C. Why the distinction between “active” sites and sites in “follow-up only?”

If a site is still enrolling and/or has active subjects, WIRB will provide the site with an updated consent form with instructions for how subjects can contact WIRB if they have questions about their rights as a research subject or with questions, concerns, input, or complaints about the research. Alternatively, if the site’s subjects are all in “follow-up only” status, WIRB will review the existing consent form for completeness, and if it is compliant with the regulations, will accept the existing consent form and provide a letter for the site to give to subjects notifying them of the change of IRB.

D. Recommended instructions for institutions deactivating their IRB or transferring multiple projects to WIRB:

1. Plan a conference call with WIRB to discuss preliminary steps toward transition of studies.
2. Begin to assess which studies have active subjects which will need to be transitioned first.
3. Begin to assess continuing review schedules which may necessitate immediate transfer to keep those studies open for active subjects. (Plan to keep the existing IRB functioning until all open studies have either closed or been approved by WIRB.)
4. Notify WIRB of the number of studies that are to be transitioned.
5. Communicate to the research community the plan to transfer active studies to WIRB.
6. Communicate to the research sponsors the plan to transfer active research to WIRB - notifying them of impending change with request for payment of transfer, and give the sponsor a deadline after which transfer will take place.
7. Establish a date for a startup meeting with a WIRB representative, if necessary or desirable, depending on staff familiarity with WIRB forms and systems, or volume of studies.

10. The review process

A. Board Actions

The Board may take a variety of actions upon review of a submission.

i. Approve

When the Board takes an “approve” action on new research (or a change in research), it is accepting oversight (or continued oversight) of the research and allowing the research to go forward as approved.

When the approval is based on Board-required consent form modifications, the investigator will be provided with a finalized consent form with the required modifications incorporated by WIRB staff. When the approval is based on Board-required modifications to other materials, the investigator is responsible for incorporating the

changes prior to using the materials. Such modifications will be indicated on the items or in a letter.

Approval is usually communicated to the investigator by a Certificate of Approval (COA).

Upon approval of a new study, the following are prepared and sent to the PI, Sponsor or CRO, SMO, and institution (as applicable):

A Certificate of Approval

A copy of the Board-approved consent form (when applicable), ready for use.

Depending on the type and extent of the Board's changes, a redline of the changes to the consent form. Redlines annotated with codes are accompanied by the legend "Reasons for Change."

Explanatory letters, if directed by Board or otherwise necessary. Letters are used to communicate special Board determinations, requirements, or other necessary information.

Explanatory notices relevant to the review.

ii. Approve with Conditions

Approval with conditions means the Board has reviewed a submission and determined it meets the requirements for approval but requires specific changes to the study and/or study documents as outlined by the Board before final approval can be provided:

1) You will receive written notification of the conditions promptly after the review.
2) Once you submit the requested information, then your submission will be re-reviewed. Once that review is complete and all information is confirmed, you will receive your approval documents.
3) It is important to note that the study, change in research, or other submitted material **is not approved until we confirm that any/all of the condition(s) have been satisfied**. This process does not allow you to begin research-related activities until you receive your final approval documents.

iii. Approve in Principle

An "Approve in Principle" action is only used when a federal funding agency requires IRB approval before grant monies can be released, and the investigator does not have the funding to complete the research proposal until the grant monies are released. The Board takes this action if it appears the research will be acceptable when the proposal is completed. The Board's determination is communicated by letter (no Certificate of Approval issued), and does not grant approval for initiation of activities involving human subjects. Upon completion of the research proposal, the protocol, consent form, and other required elements must be submitted to WIRB and approved before activities involving human subjects can begin.

iv. Disapprove

When the Board takes a "disapprove" action on new research, it is rejecting oversight of the project as submitted, and the research is not allowed to go forward.

When the Board takes a “disapprove” action on a change in research, the change cannot be implemented, and the Board expects the research will continue as previously approved.

Disapproval may occur for a variety of reasons, most of which involve subject safety and/or scientific validity. Disapproval is communicated to the investigator by letter, in which the reasons for disapproval are explained.

Reconsideration of a disapproval may be requested and is taken to the same panel which voted the disapproval. Additional information may be provided to the Board for its consideration. The investigator may appear before the Board in person or via teleconference, if desired.

v. Defer

The Board takes a ‘deferred’ action to remove an item from Board consideration at a scheduled meeting and obtain additional information or clarification. Staff and/or Board members follow up as directed with the investigator or sponsor to address the reasons for deferring the item. Staff prepare the item and reschedule it for the Board to complete its review. A tabled item is brought back to the same panel that tabled it. Additional information may be provided to the Board for its consideration. The investigator may appear before the Board in person or via teleconferencing, if desired.

Some of the common reasons for Board deferring an item are discussed below:
Incomplete submissions and inaccurate information. If answers on the WIRB submission form are left blank, the answers don’t make sense, or they conflict with the protocol, the Board is unable to make an appropriate decision and may defer the item to request further information.

- **Protocol allows legally authorized representatives (LARs) to consent for subjects when not ethically appropriate.** Sometimes protocols contain standard language stating that the subject or their LAR may consent to research, even when the research can be ethically conducted using only capable subjects who are able to consent for themselves. The Board bases its decision on the basic ethical principle that research studies should only enroll subjects who do not have full mental capacity when the study cannot be conducted in any other way, unless there is a significant prospect of direct benefit to those subjects that is not otherwise available. Please make sure that your protocol does not unnecessarily include incapable adult subjects.
- **Not all members of the research team have completed training in human subjects protection.** WIRB requires that all investigators and their research staff complete human subject protection training prior to submitting to WIRB. (HIPAA training alone is not sufficient.) More information about available training in human subject protection is available in the section of this Guide titled “Requirements for Human Subject Protection Training”. [Since treatment use INDs and treatment use IDEs (as defined at 21 CFR 312.34 or 21 CFR 812.36) are not “research” in the usual sense, physicians requesting approval of single-

patient treatment use INDs and IDEs are generally exempt from this requirement.]

- **Local law requirements are not met or prevent conduct of the research.** The Board may defer a submission when specific local law requirements are not met. For example, there are requirements that must be met when a study conducted in New Jersey involves incapable adults. If the additional requirements are not met, the Board must defer the study. The WIRB Initial Review Submission Form contains extra instruction for investigators in those states that have additional regulatory requirements that need to be fulfilled prior to Board approval.
- **IND or IDE issues.** One of WIRB's requirements is that IND and IDE requirements are satisfied. Some submissions received by WIRB need an IDE or IND and do not have one. For more information on IDE and IND requirements, please see the sections of this Guide titled "Special considerations for Drug Research: Do you need an IND?" and "Special considerations for Device Research".
- **Emergency plans or hospital privileges not sufficient.** The WIRB Initial Review Submission form asks for information about the facility to be used in an emergency and whether the PI or sub-investigator have staff privileges at the facility. When subjects may experience medical emergencies related to their participation in the research, if the answer is no, WIRB requires a plan be submitted that describes how subjects will be referred for hospitalization, contact information for a physician that has agreed to attend to these patients and a description of what measures will be used to assure communication between the investigator and the attending physician.
- **Risks to subjects outweigh benefits.** The Board provides a letter outlining the reasons why the risk to benefit ratio was determined to be unacceptable.
- **Scientific validity is lacking.** The Board provides a letter outlining the reasons why it determined that the research lacked scientific validity.
- **Justice issues.** Board will consider whether groups are inappropriately included (such as pregnant women, mentally incapable persons and children) or are inappropriately excluded (like women or minorities) from the research.
- **Consent issues.**
    - **Consent in emergent setting.** In emergent settings, subjects have limited time and are often impaired in their ability to make informed decisions about participating in research. The Board gives special consideration to the consent process when it will take place in an emergency setting and requires that an acceptable process be in place for obtaining consent. WIRB's initial review submission form requests detailed information about the consent process in emergent settings.
    - **The process for obtaining consent over the Internet or telephone is not sufficiently explained.** WIRB must be assured that the elements of consent required by the regulations are still addressed and that security and privacy concerns are addressed.
    - **Request for waiver of consent or waiver of documentation of consent not adequately justified.** There are certain regulatory requirements that

need to be met for waivers of consent and waivers of documentation of consent to be acceptable in research. WIRB has specific forms used to collect information about waivers of that will help the Board determine if the waiver is appropriate. More information about the requirements for waivers can be found in this Guide in the sections titled "Waivers of Consent" and "Waiver of Documentation of Consent".

  - **Consent of secondary subjects is not addressed.** When the project proposes the collection of information about an individual from someone else (for example, medical information about an identifiable relative of the subject) without direct contact with the individual, that individual may be considered a "secondary subject" and consent (or a waiver of consent) for that individual needs to be considered. For more information, please see the OHRP guidance titled "OHRP - Guidance on Research Involving Coded Private Information or Biological Specimens" available online here: http://www.hhs.gov/ohrp/policy/cdebiol.html. (The guidance does not include a direct statement about secondary subjects but discusses whether the collection of private identifiable information of a relative meets the definition of human subject.)

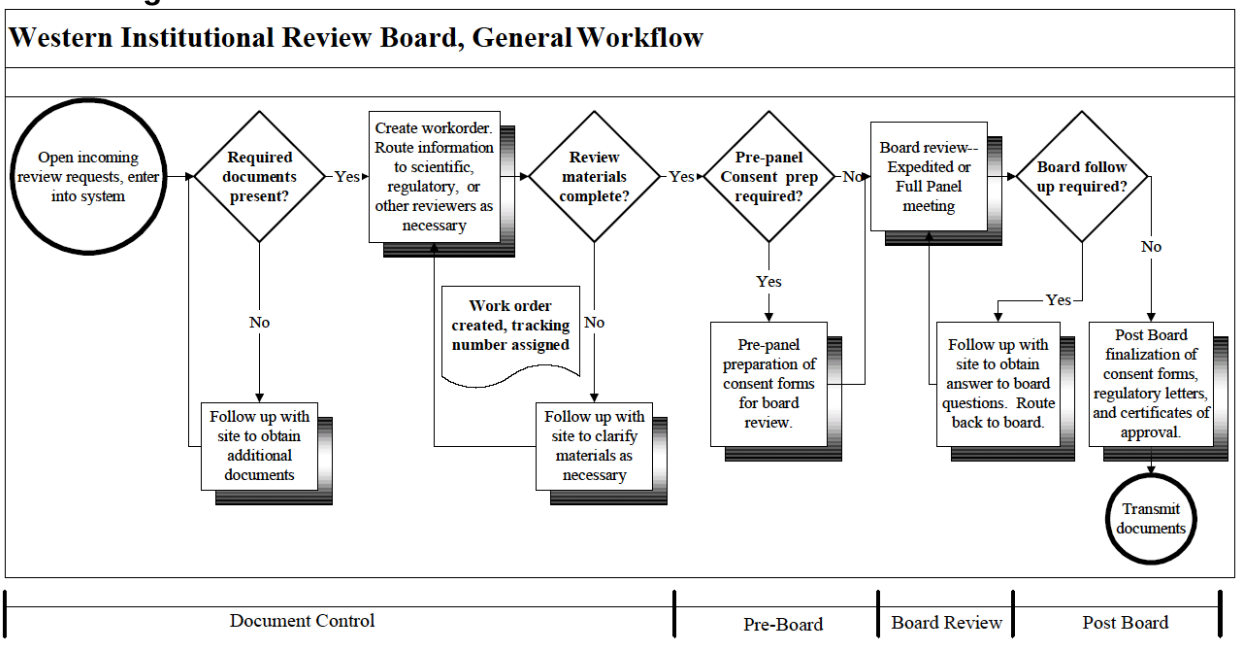
- **Recruitment issues insufficiently addressed or not addressed.** The most common issues the Board encounters with subject recruitment methods are outlined below:
  - Screening scripts that do not contain the required information, or are not accompanied by the WIRB Screening Procedures Information Form. WIRB's screening requirements are outlined at the end of its Screening Procedures Information Form.
  - Cold calls. As a general principle, when potential subjects are being recruited for research based on a review of their non-public medical information, the contact should be initiated by a clinical provider who has had a provider relationship with the potential subject.
  - The process for recruitment of subjects is not described at all.
- **Inconsistency in documents.** If during review of the submitted documents (protocol, consent forms, advertisements), the Board finds inconsistency either within the documents or between documents, they may defer the submission and request clarification of the inconsistencies.
- **Consent forms.** The Board can make changes to the consent form. However, some consent forms cannot be fixed by Board when:
  - The consent form and protocol are not consistent (for example, the consent form cites additional procedures not included in the protocol, such as additional blood draws or collection of tissue samples for future research; or the consent form was developed from another protocol and there is language in the consent form that is left over from the other protocol).
  - The information in the consent form is internally inconsistent (for example, the compensation for injury text provided by the sponsor conflicts with the compensation for injury text required by the investigator's institution).
  - The consent form is poorly written and requires extensive changes.

vi. Pull

The Board may "pull" an agenda item at the request of the submitter, WIRB staff, or the Board itself. An item generally is pulled before the Board begins consideration of the item in a meeting due to missing or incomplete review information.

Staff and/or Board members follow up as directed with the investigator or sponsor to address the reasons for pulling the item.

B. Diagram of WIRB Workflow



11. Changes to Research / Additional Document Submissions

A. Changes to Research

Whenever a **change to the protocol or consent form** is proposed, the change must be reviewed and approved by WIRB before being implemented, unless a serious safety concern requires immediate implementation by the investigator.

You may use the WIRB **Change in Research Submission Form** to submit requests for review of changes to protocols, consent forms or subject materials; review of new consent forms and subject materials; or review of new or modified recruitment materials.

i. How to submit a protocol change

Requests for review of protocol changes must include the exact text of the amendment, administrative change, or other revision to the protocol, a summary of changes, the rationale for the change, and a copy of the WIRB-approved consent form with the proposed changes clearly marked (if applicable).

Proposed changes to the consent form should be "redlined" into an electronic copy of **the current WIRB-approved consent form**. In order to facilitate the submission of consent form changes, WIRB now routinely provides sponsors and CROs with a clean copy of each WIRB-approved consent (without site specific information in it). WIRB does not recommend marking changes with a highlighter alone, as the highlighting can be lost or obscure information when the document is scanned into WIRB's electronic workflow system.

ii. How to submit a consent form modification

Requests for consent form modifications should consist of an online submission through WIRB's smart form feature or the WIRB **Change in Research Submission Form**, and a copy of the WIRB-approved consent form with proposed changes clearly-marked (or a document specifying the requested changes). Proposed changes to the consent form should be "redlined" into an electronic copy of the current WIRB-approved consent form. In order to facilitate the submission of consent form changes, WIRB now routinely provides sponsors and CROs with a clean copy of each WIRB-approved consent (without site specific information in it). Changes sent to WIRB on the *sponsor's* template consent form will not be accepted.

WIRB does not recommend marking changes with a highlighter alone, as the highlighting can be lost or can obscure information when the document is scanned into WIRB's electronic workflow system.

In general, a statement justifying changes is very helpful and can reduce the need for WIRB to contact sites for explanations. Whenever revisions are requested to previously Board-approved language, the submission must include a rationale, and changes to study procedures that are described in the consent form must be supported in a revised protocol.

We recommend using the "smart" online form available via Connexus® (https://connexus.wcgclinical.com/default.aspx). The "smart form" submission is generally a shorter process because it dynamically omits questions that are not relevant, based on the answers you provide about the research. Documents submitted for review can also be uploaded securely from the WIRB web site, mailed, or e-mailed (clientservices@wirb.com). Submissions should reference the sponsor protocol number, WIRB study number, and name(s) of applicable investigator(s).

If the changes are to be submitted for a multi-site study, the same changes might have already been approved by WIRB for another site. If you agree to accept the changes already approved, your review will take place more quickly. You can contact WIRB Client Services to determine if pre-approved language exists for your change in research.

iii. How to Request a Reconsideration

Requests for a ***reconsideration*** of a Board action must be accompanied by a rationale for the request. Additional information may allow the Board to favorably respond to the request. There is no additional fee for reconsiderations of disapproved items. Likewise, reconsiderations of board-directed modifications to consent forms and other subject materials or recruitment materials do not incur additional fees if the reconsideration is in regard to the language *originally reviewed* by the Board. If new or alternate language is submitted, the Change to Research fee applies.

iv. How to Submit a Change of Principal Investigator

The Board requires written confirmation from the sponsor that the change is acceptable and has been approved, and a letter from the old investigator relinquishing responsibility for the study is required (or an explanation for why one is not available – please note that if the current investigator has not been overseeing the study, WIRB will also need to know how long the PI has been gone, who has been overseeing the study in the PI's absence and if there have been any subject safety concerns during this time). The Board expects departing PIs to arrange for an orderly transition of their research to the new investigator. The sponsor is required to select investigators under 21 CFR 312.53(a).

Also submit a WIRB **initial review submission form** , license, and CV for the new investigator (unless current versions are already on file with WIRB), and a request to modify the existing consent form to reflect the new investigator's name and contact information (when applicable).

Once approved, the new PI is authorized by WIRB to carry out the study as previously approved for the prior investigator (unless the Board provides alternate instructions to the new PI). This includes continued use of the previously approved study materials (consent form, recruitment materials, subject materials, and so forth).

v. How to Submit an Updated Drug Brochure

Updated drug brochures should be accompanied by a summary of changes, a cover letter identifying the name of the Principal Investigator, the drug, and the WIRB protocol and study numbers.

B. Additional changes which require submission to WIRB

- Notify WIRB of changes of address or telephone for the investigator or the site(s) **before the move**. (If you are adding a site or moving to a new site, complete an online smart form submission or download and complete a WIRB Change in Research and Subject Recruitment Submission Form and an Additional Site form for each new or updated location and forward to us. Please note that those two forms will be retired December 21, 2015 and replaced with a single Change in Research smart form available on the WIRB website.)
- Notify WIRB of changes of address, or telephone for study or sponsor contacts.

- Request review of increases in the number of subjects allowed at the specific investigator site (indicate if a consent form change is needed).

Minor administrative changes sent to the investigator from the sponsor generally should be submitted to WIRB for review as "Administrative Letters" or "Administrative Changes." This type of change might consist of sponsor notifications of changes to the status of the protocol (such as completion of enrollment, completion of a cohort, ending development of a test article).

The above list is not an exhaustive listing of the changes in research that may need to be reported to WIRB. If you are in doubt about submitting a particular item, call Client Services at 1-800-562-4789 or e-mail clientservices@wirb.com.

C. Subject Recruitment Materials (Ads, etc.)

Complete the WIRB "**Change in Research and Subject Recruitment Submission Form**" to submit advertisements for review after initial review of the research (please note that that form will be retired December 21, 2015 and replaced with a single Change in Research smart form available on the WIRB website). As much as possible, print ads should be submitted as they will appear in print, so that the Board can assess the impact of design details, such as photographs, other images, and font sizes and styles.

WIRB does not allow **referral fees** (offering or accepting payment for referring patients to research studies, sometimes referred to as "finder's fees") for medical professionals or research staff. Payments to subjects for referring others may be considered by the Board on a case-by-case basis. This is in accordance with the American Medical Association Code of Medical Ethics which states, "Offering or accepting payment for referring patients to research studies (finder's fees) is also unethical." Some states have laws that ban such practices.

Most changes to approved advertisements must be reviewed by WIRB prior to their use, particularly anything that could alter the impact of an advertisement previously reviewed by the Board. Changes to approved advertisements that do not need to be submitted for review include updates to phone numbers or contact names referenced in an advertisement and corrections to spelling.

For best results, when submitting subject recruitment materials or other subject materials (diaries, questionnaires, etc.) that have been previously reviewed by WIRB, state in the cover letter that the items have been previously reviewed by WIRB. WIRB support staff will provide the Board with information about the previous Board review, so that the previous decision of the Board will be taken into account when the materials are reviewed.

Information packets, patient brochures, sponsor brochures and informational videos are all considered recruitment materials if they are intended to be seen by a *potential* subject.

Audio and Video Recruitment Materials: All audio and video materials should be accompanied by the script.

To avoid unnecessary additional production costs due to re-work, it is strongly recommended that WIRB approval of scripts for planned audio or visual recruitment materials be obtained *before* producing the spots. Any Board-required modifications to the material must be reflected in the final version of the recording.

When audio or video scripts are sent to WIRB for review, WIRB pre-reviews the script and, if acceptable, approves it with modifications or as submitted. . The submitter receives a copy of the script displaying the Board's required modifications, if any. The final recording must be submitted to WIRB for final approval before use with subjects and MUST match the WIRB approved script. Submit a copy of the corresponding script when you send the recording to WIRB for review.

Ads for all sites: Advertisements which will be used by some or all participating investigators should be identified as such in the cover letter or submission form. Identifying shared advertisements as such will help ensure consistent review of materials for all participating sites.

Press Releases: WIRB reviews submitted press releases as advertising. **Do not submit press releases for which you do not desire WIRB review.**

Logos: If the Board considers elements of a logo in an advertisement to be coercive or overly reassuring, they will direct that the logo be removed from the ad or be modified to eliminate the objectionable element(s).

Public service announcements and phone system "on hold" messages: Public service announcements and audio scripts of messages that will be broadcast to callers who have been placed on hold are considered recruitment materials, will be reviewed by the Board and, if acceptable, approved either "as submitted" or "as modified."

Website Content: WIRB review requirements for web content are dependent on the type of content in question --

- ClinicalTrials.gov-type sites which provide a limited set of pre-formatted fields for inclusion of recruitment content do not need to be submitted for IRB review. If requested, WIRB will review submissions of such content. FDA Guidance regarding use of media advertising to recruit subjects can be found at http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting.

- Subject recruitment content on sponsor websites requires IRB review. **Only the content relevant to research should be submitted for review.** It may be appropriate to request WIRB review of these materials as "generic" recruitment

materials (for more information about generic reviews, see the section of this handbook titled "Review of "Generic" Materials"). The content should not be posted until WIRB has approved it.

- Subject recruitment content on investigator or SMO websites requires IRB review. **Only the content relevant to research should be submitted for review**. The content should not be posted until WIRB has approved it.

Only content pertaining to research needs to be reviewed by the IRB; submit to WIRB only website content which provides information to potential subjects about research participation, as well as information about specific studies that WIRB oversees. General website information that does not relate to research participation, such as disease information or driving directions to the research office, does not require review.

WIRB does not review the content of the links to other websites that are present on submitted websites. The website owner should ensure the links are appropriate.

The web owner is responsible for making the Board-directed changes to reviewed website content before using that content for recruitment.

Changes made to approved website content should be submitted for Board review **before the changes are posted to the web**.

Website content can be reviewed either in relation to a specific protocol or as generic recruitment material. If the material is reviewed and approved as a "generic," an expiration date is assigned (usually a year from the approval), and the Board conducts re-review of the content when the expiration date approaches unless WIRB receives a request to close the file.

Recruitment materials that WIRB does not review

The FDA Information Sheets state:

> Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects. **Not included** are: (1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

Based on this guidance, WIRB does not require IRB review of doctor-to-doctor letters, or prior IRB review of interviews with the media (as noted previously, this does not apply to "press releases") and there is no need to provide WIRB with copies of these materials.

D. “Do’s” and “Don’ts” for Recruitment Materials (Advertising)

Over time, WIRB has developed standards for ad review that are consistent with federal guidance on recruitment materials, and serve to maintain consistency in the Board review of these materials. The following points summarize these standards and serve as a guide to Board changes or disapprovals of recruitment materials.

Do:

- The advertisement should clearly indicate that it concerns a research study. Use of words such as “investigational,” “experimental,” “clinical trial,” and “research” are an acceptable way to do this.
- The advertisement should comply with the guidance in the FDA Information Sheet, "Recruiting Study Subjects."

Don’t:

- Do not state or imply that the FDA or IRB has approved the research.
- Do not refer to investigational drugs, devices, or procedures as "new," "safe," "effective," "a cure," "treatment" or "therapy," without qualifying them with “investigational,” “experimental” and so forth; for example “new investigational drug.”
- Do not call the investigational medication simply "medication" or "drug"; qualify each use appropriately with "investigational" or "study" as in "investigational medication" or "study medication."
- Do not emphasize payment to subjects or the word "free" (e.g., bold, large font, dollar signs).
- Do not include payment amounts for studies involving underage subjects.
- Do not use the terms "confidential" or "completely private."
- Do not include exaggerated statements about the potential benefits of participating in the research, receiving treatment from the investigator, or receiving treatment from the organization.
- Do not include inappropriate promises of benefit.
- Do not use the phrases "Enrollment limited," "Study ends soon," or "Call today!"
- Do not include the statements "You deserve to feel better," "Join this study and take charge of your life," or similar phrases or logos.
- Do not include references to website recruitment content that has not been reviewed and approved by an IRB (except the clinicaltrials.gov website and other such public registries).
- Do not include statements of implied safety and/or efficacy.
- Do not include misleading content.
- Do not use potentially coercive or reassuring graphics, pictures, fonts or symbols.

E. WIRB Requirements for Screening Materials

Submitted screening materials should conform to the following Board requirements.

Introductory Statement:

- The screening script must include an introductory statement that informs the subject of the purpose of the questions and that they do not have to answer any questions they do not want to answer.
- The script must not describe the type of questions that will be asked as "confidential;" i.e., rather than saying "we would like to ask you some *confidential* questions," say "we would like to ask you some questions." It is acceptable to say "personal questions" or "sensitive questions." The purpose of this policy is to prevent any possible misunderstanding that the answers will be held in complete confidence.
- When appropriate, the script must include an introductory statement warning the subjects of the sensitive nature of the questions that might make the subject uncomfortable, and preferably include an example (for instance, "We are going to ask you about drug or alcohol use.") This will generally be limited to questions about mental illness, substance abuse, and sexual abuse. For these types of screening scripts, it may be appropriate to not collect any identifying information until after the questions are asked; i.e., collect the name and other identifying information at the end of the conversation and the form.

Here is a sample introductory statement:

> [Thank you for calling] (or) [We are returning your call] about a research study we will be doing. The purpose of the study is [briefly describe study - such as,
> ". . . to evaluate the safety and effectiveness of an investigational drug for arthritis"]. Participation in this study would last about [number of days, weeks, etc.] and (if applicable) would require up to [number] of visits to our office.
>
> To see if you might qualify for this study, I need to ask you some questions about your health history and present condition. Some of these questions may be sensitive, such as questions about [give examples - such as, drug use, birth control, mental health, sexual activity, etc.] You do not have to answer any questions you do not want to answer. You may stop this interview at any time. If you do not qualify for this study, the information you give me will be [such as, "destroyed immediately" or "stored (where and for how long)"]. Do I have your permission to proceed?"

Body of Screening Form

- The Board expects to see the actual questions that will be asked, not just a general statement such as "inclusion/exclusion criteria addressed."

Closing Statement

- The script must include a closing statement informing the subject of whether or not they have met the preliminary screening requirements.

- The script must address in a closing statement whether the information received from the subject will be destroyed immediately, or whether it will be stored, and if so for how long and where.
- If the site would like to keep information for future contact for new studies, the site should describe that to the subject as well, and the subject must have an opportunity to decline.

Additional Issues

- The screening script must be in language understandable by lay people. If complicated medical terms must be included in the screening script, please provide WIRB with an explanation of how they will be explained to the subjects.
- WIRB realizes that the script may not be followed verbatim, as subjects may ask additional questions or stray from the topic. This is acceptable, but WIRB expects that the interviewer will keep as closely as possible to the spirit and letter of the script.
- It is useful to WIRB if the investigator informs WIRB of the use of the recruitment screen; such as, if it is going to be used with subjects calling in from advertisements, for calling patients listed in a database, or for conducting cold calls.

12. Review of "Generic" Materials

"Generic" materials include items that an investigator would like to use outside of the context of a specific protocol, or materials that a sponsor/CRO/SMO would like to use that do not identify any one specific investigator and/or protocol. Common types of generic materials include:

- Generic Advertising, including Brochures, audio-visual materials, Web Content
- Generic Pre-Study Screening Consent Forms
- Generic Telephone Screening Scripts
- Generic Consent for Photography

A. Generic Consent Forms

Generic consent forms should contain all the usual consent form elements defined in federal regulations and guidance (see section titled Consent Form Elements). As much detail as possible should be included. Many times general research participation information will be included, with a listing of types of research the investigator is conducting.

WIRB imposes the following limitations on generic consent forms:

- Pre-study screening done outside of a specific research protocol should be limited to minimal risk procedures.
- Current treatment or medications should not be adjusted in order to do the screening.

Accordingly, prospective subjects should not undergo a washout or biopsy as a generic pre-screening activity; instead, the subject should be fully consented for the related protocol before beginning that protocol's screening activities.

B. Generic Advertisements

WIRB reviews "generic" advertisements linked to a company or an investigator and protocol-specific generics that do not contain any site-specific information. Approval documents for generic advertisements are transmitted to the submitter; courtesy copies of generic advertisements will not be distributed to multiple sites or investigators.

Unless subjects at all sites (and/or participating in all protocols) receive the same payment for every study visit, it is wise to omit dollar amounts from generic advertisements. A general statement such as "subjects will be paid for their participation" is recommended instead.

Changes to approved generic materials must be reviewed and approved before use.

C. Expiration and Renewal of Generic Materials

Approved generic items are generally valid for one year. When the anniversary date approaches, WIRB staff will contact the submitter and inquire if renewal is desired. WIRB will conduct an annual review of the item if a response is not received by the date cited in the correspondence to ensure continued use is valid and under IRB oversight. Study Renewal Review fees apply. Expired generic items cannot be used. To prevent unnecessary renewal reviews, notify WIRB when use of the generic material has ended.

Occasionally, the Board may modify an item during the renewal review, usually due to changes in regulatory guidance or Board policy. Board-directed modifications are indicated in the approval documentation provided to the submitter.

13. WIRB reporting requirements

A. "Promptly Reportable Information" form

Use the WIRB "Promptly Reportable Information" form to report the following information to us within 5 days:

1. New or increased risk
2. Protocol deviation that harmed a subject or placed subject at risk of harm

3. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
4. Audit, inspection, or inquiry by a federal agency
5. Written reports of federal agencies (e.g., FDA Form 483)
6. Allegation of Noncompliance or Finding of Noncompliance
7. Breach of confidentiality
8. Unresolved subject complaint
9. Suspension or premature termination by the sponsor, investigator, or institution
10. Incarceration of a subject in a research study not approved to involve prisoners
11. Adverse events or IND safety reports that require a change to the protocol or consent
12. State medical board actions
13. Unanticipated adverse device effect
14. Information where the sponsor requires prompt reporting to the IRB

Information not listed above does not require prompt reporting to WIRB.

In early 2014, WIRB discontinued asking research sites to determine if an event constituted an "unanticipated problem" as defined by the regulations; instead, WIRB create a new, easier to use, single Promptly Reportable Information form that provides sites with categories of information to report to WIRB in a prompt manner.

Please note, consistent with AAHRPP's requirements in connection with its accreditation of IRBs, the individual and/or organization submitting research for review shall promptly communicate or provide, and where necessary cause each investigator to promptly communicate or provide, the following information relevant to the protection of human subjects to WIRB in a timely manner:

a. Upon request, a copy of the written plan between Client and Site that addresses whether expenses for medical care incurred by Human Subject Research subjects who experience research related injury will be reimbursed, and if so, who is responsible in order to determine consistency with the language in the consent document.

b. Any site monitoring report that directly and materially affects subject safety or their willingness to continue participation. Such reports will be provided to the Review Board within 5 days.

c. Reports from any data monitoring committee, data and safety monitoring board, or data and safety monitoring committee in accordance with the timeframe specified in the study protocol.

d. Any findings from a closed study when those findings materially affect the safety and medical care of past subjects. Findings will be reported for 2 years after the closure of the study.

B. Planned Deviations

Please note that planned deviations should be submitted to WIRB as a change in research for federally funded research and FDA drug and biologic studies. The WIRB Certificate of Approval for recent studies states:

- Investigators are instructed to obtain pre-approval from WIRB for planned deviations and changes in research activity as follows:
    - If the research is federally funded, conducted under an FWA, or is a clinical investigation of a drug or biologic, then all planned protocol deviations must be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].
    - However, if the research is a clinical investigation of a device and the research is not federally funded and not conducted under an FWA, then only planned protocol deviations that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data should be submitted to WIRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].

    The reason for these different requirements regarding planned protocol deviations is that the Office for Human Research Protections (OHRP) and the Food and Drug Administration (FDA) drug and biologic divisions have adopted the regulatory interpretation that every planned protocol deviation is a change in research that needs prior IRB review and approval before implementation; however, the FDA device division operates under a distinct regulation (See 21 CFR 812.150(a)(4).

14. Overview of WIRB's continuing review activities and required reports

A. Continuing Review

During the initial review of a protocol, the Board makes a determination on the required frequency for reporting information related to the research.

FDA regulations regarding continuing review require an IRB to conduct continuing review of the research at intervals appropriate to the degree of risk, but <u>not less than once per year</u> [21 CFR § 56.108 (a)(1) and § 56.109(f)]. For a few types of research, however, full board review is conducted more frequently than once a year. The Board normally determines that a full review of phase I research, investigator-initiated single-site interventional studies of investigational drugs and devices, emergency research conducted under 21 CFR 50.24, and child research conducted under 45 CFR 46.407

should be conducted every six months. The Board may also direct more frequent than annual review for other research as deemed appropriate.

i. Site Reporting:

Completed Continuing Review Report Forms (CRRFs) provide WIRB with the study-related data necessary to monitor the progress of the research at sites. WIRB sends sites a CRRF three weeks prior to the due date listed on the form. Identifying information including investigator name, sponsor name, protocol number and the "sequence" number of the form is listed at the top of each form. The CRRF is sent out approximately 50 days before the study's expiration date, in order to ensure it is completed and sent back to WIRB before the Board conducts the study renewal review. The Board may take action to suspend or terminate approval of the research if a report is not accurately completed and returned promptly.

CRRFs must be filled out completely and returned to WIRB in a timely manner. Even if the site has not started enrolling subjects, the site must complete the CRRF and return it to WIRB before the due date printed on it, to inform the Board of the study's status at the site.

Before sending a completed report form to WIRB, verify that the reported data (specifically, enrollment numbers) do not conflict with any previous reports to WIRB. WIRB will not accept data inconsistent with prior reports. If reported data conflicts with the previous report, WIRB will contact the site to obtain corrected information. This may hinder study renewal.

ii. Sponsor Reporting:

Before each annual review, WIRB sends out a Protocol Progress Report to the sponsor or CRO contact we have on file. The Protocol Progress Report is designed to collect protocol-wide data as recommended in the FDA guidance document titled "IRB Continuing Review after Clinical Investigation Approval." In this guidance, FDA recommends several times that both central and local IRBs should obtain and review protocol information. We are asking you to complete and return the attached Protocol Progress Report before the due date indicated on the form. The individual study sites will continue to receive separate site progress reports to complete and submit as well.

We want to make the PPR process as efficient as possible for all parties. Therefore, WIRB will accept receipt of the completed PPR form from any party. In addition, FDA notes in the guidance that existing sponsor reports containing the requested data could be re-purposed for the purposes of reporting protocol-wide information to the IRB, such as annual Progress Reports or the Development Safety Update Reports (DSUR) Executive Summary. WIRB is quite flexible as to the format in which we receive this information, and we will happily accept other reports that provide the same basic information.

The Protocol Progress Report is sent out approximately 50 days before the protocol's expiration date, in order to ensure it is completed and sent back to WIRB before the Board conducts the study renewal review. The Board may take action to suspend or terminate approval of the research if a report is not accurately completed and returned promptly.

i. Continuing Review Report Form (CRRF) Work Sheet:

The CRRF Work Sheet is a guide to completing the WIRB CRRF for study coordinators and PIs (see next page).

A guide to completing the WIRB CRRF for study coordinators and PIs

1. *AT YOUR SITE: Has the study begun?*

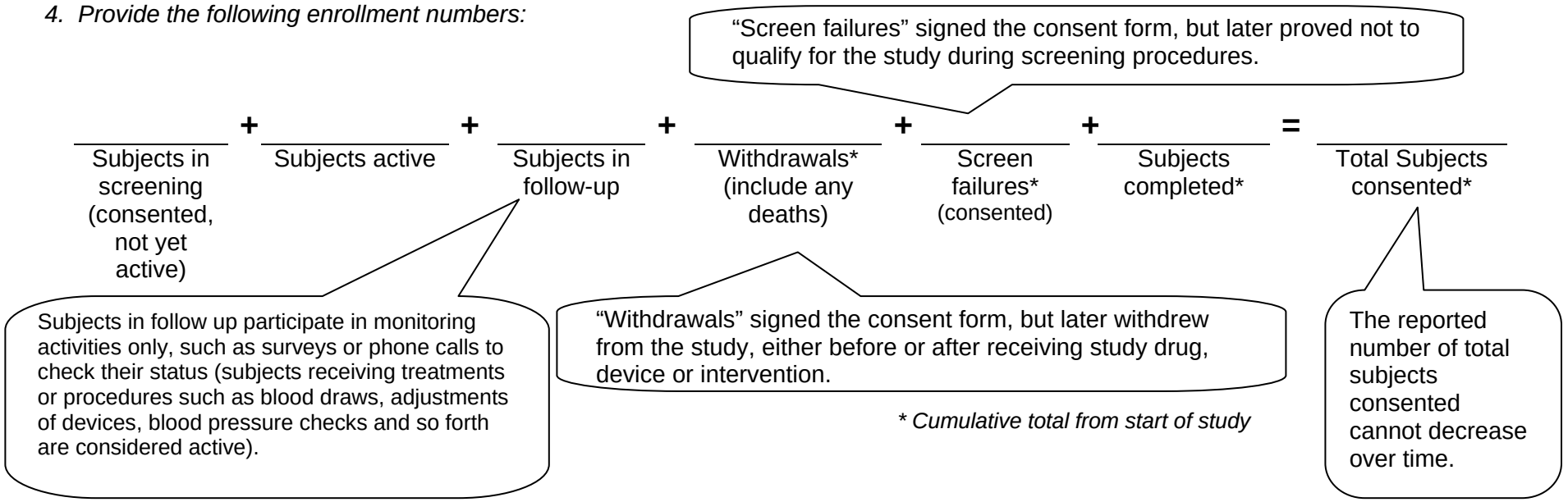
   If no, skip to the next question indicated on your form.

2. *If this is the first report submitted since a subject has consented to participate, attach a signed WIRB-approved consent document.*

   You may mark "NA" if you have already submitted a signed consent form, or if WIRB approved a waiver of consent or waiver of documentation of consent for all subjects.

   Subjects should be signing the clean version of the most current WIRB-approved consent form (redlined consent forms are provided for reference purposes only).
   If the study at your site is under the oversight of another IRB in addition to WIRB, send only a signed copy of the WIRB-approved consent form.

4. *Provide the following enrollment numbers:*



5. *Number of females consented* _____

6. *Number of racial minorities consented: _____*

Federal regulations require IRBs to gather information about the racial makeup of the subjects in the study.

7. *Approximate racial makeup of consented subjects: (must add up to exactly 100%)*

White: _____%	Black or African American: _____%
Asian: _____%	Native Hawaiian or other Pacific Islander: _____%
Other: (specify) _____%	American Indian or Alaska Native: _____%

8. ***AT YOUR SITE:*** *Have there been any unanticipated study-related problems that involve risks to subjects or others which have not previously been reported to WIRB? If yes, complete and attach the appropriate WIRB reporting form.*

Detailed instructions and forms for reporting are available at www.wirb.com.

9. ***AT YOUR SITE:*** *Have there been any subject withdrawals which have not been previously reported to WIRB? If yes, indicate the reasons for the withdrawals.*

"Withdrawals" signed the consent form, but later withdrew from the study, either before or after receiving study drug, device or intervention.

10. *Does the scientific literature indicate changes in knowledge relevant to the conduct of the study? If yes, attach a brief summary of the information.*

The summary should include a brief description of any changes in the currently accepted therapy or practices utilized in the protocol. Study coordinators should request a response from the Principal Investigator, who should be aware of relevant changes in the standard of care.

11. *Is there new **risk** or **benefit** information **not previously** reported to WIRB? If yes, attach a copy.*

These might be data safety monitoring reports or other updates to risk or benefit information related to the study.

12. *Are there changes to the protocol or consent form or other material seen by subjects **not previously** reported to WIRB? If yes, attach a copy.*

Attach an explanatory letter and the changes, or fill out and submit the WIRB Change in Research Submission Form available at www.wirb.com.

13. *Have you received any subject complaints since your last report?*

If yes, summarize the complaint(s) (attach additional sheet if necessary).

14. Is the PI aware of any changes in state or local laws related to research? If yes, attach appropriate information.

A letter of explanation may be attached. The letter does not have to specify the exact change if the submitter is not entirely familiar with the change.

15. What is the PI's perception of the community's attitude toward research? If negative, please attach an explanation.

An explanatory letter may be attached, as well as applicable news clippings, etc., as applicable.

*16. Is the PI aware of any recent events **in his/her community** (such as deaths or serious injuries) related to research? If yes, please attach any information you may have about the event.*

An explanatory letter may be attached or just the applicable news clippings, etc.

17. Investigators must ensure each member of the research study team/staff has had training in the protection of human subjects. Have you added new study staff since your last report?

New team members must complete human subject protection training.

HIPAA training alone is not sufficient. WIRB's expectation is that training include topics such as ethical principles related to human subject protections, federal regulations for protection of human subjects, and Good Clinical Practice. A list of potential sources, including web-based tutorials, in-person trainings, and books, is available at www.wirb.com or by contacting WIRB's Client Services.

*18. Have you been audited for **any study** by the FDA or OHRP since your last report? If yes, date of audit: _____. Please submit a copy of the FDA report as soon as available (or indicate if the report has been previously provided to WIRB).*

If the FDA or OHRP has audited, but the information has already been reported to WIRB, mark "Yes" and the date of the audit, and note that the information has been previously forwarded to WIRB. International sites: please report any audits by the local regulatory agency.

19. Has the research team conflict of interest information provided to the Board since the last review changed? If yes, please attach a summary of the changes (you may fill out and attach a copy of the WIRB Financial Disclosure Form available at www.wirb.com).

Studies approved since May 2003 have been required to provide information about possible conflicts of interest with the initial review submission. If the information provided to the board at initial review or since initial review has changed, provide the updated information. WIRB recommends using the form posted on its web site.

20. Are there any current investigations or charges involving the Principal or Sub-Investigator(s)?

If yes, please attach appropriate information; if you have already reported the information, just indicate "already reported to WIRB on [date]".

21. Has the PI's medical license been renewed during this reporting period? If yes, please attach a copy.

22. Have the hospital privileges of the PI or the subinvestigators at the hospital where subjects are treated or seen in case of emergency been reduced since your last report? If yes, please explain how the change will affect the plan for treatment and/or emergency care of subjects: (attach additional sheet if necessary)

WIRB must be assured that there is an appropriate system in place in the event that a subject is hospitalized. If neither the PI nor the sub-investigators have privileges at the designated emergency facility, please describe how subjects would be referred for hospitalization, what physician(s) would assume the role of the attending, and how communication between the attending physician and the investigator would be assured. It is not sufficient to state, "They will be referred to the emergency room."

23. Is there any information you have not otherwise reported that summarizes study activity to date?

If yes, attach appropriate information.

Such information might include a data safety monitoring committee report, the sponsor's Annual Report to the FDA, or communications from the sponsor addressing study-wide issues or progress.

24. Signature of PI or designee.

Unsigned forms will be deemed incomplete, and WIRB staff will follow up with a request for a signed form.

ii. Delinquent Progress Reports (CRRFs and Protocol Progress Reports)

If a completed report is not returned to WIRB in a timely manner, WIRB sends a second copy of the missing report labeled "Reminder Notice."

The Board may take action to suspend or terminate approval of research if reports are not accurately completed and returned promptly. If WIRB suspends or terminates the study, at a minimum, the investigator and sponsor will be notified of the Board's action, as well as any federal agencies with jurisdiction over the research, such as FDA and/or OHRP.

When a report is not returned in a timely manner, WIRB takes the following action:

1. If a completed form is not received, 10 days after the due date WIRB staff prepare a "past due" notification which explains that if a satisfactory response is not received shortly, the delinquency will be reported to the Board and that the

Board may take action to suspend the study at the site. The letter is sent to the investigator, sponsor contact, institution contact (if applicable) and other study contacts.

2. If no response is received 20 days after the due date on the report, WIRB staff place a courtesy call to the sponsor notifying them of the continued delinquency and the likelihood that the Board will take action to suspend the study at the site if a response is not received.
3. If no response is received 37 days after the due date on the report, the delinquency is reported to the Board. If the Board suspends the research, WIRB is required to report the suspension to the appropriate federal agency or agencies (FDA, OHRP, etc.) If the suspended investigator is at an institution which has notified WIRB that they will self-report these actions to the appropriate agency or agencies, the institution will receive a notification of the Board's action and a cover letter reminding them of the reporting requirement. The institution has 30 days to then report to the agency and copy WIRB.

iii. Signed Consent Form Requirement:

The WIRB CRRF states "If this is the first report submitted after you have begun to enroll subjects, you must enclose a copy of a WIRB-approved consent document, signed by an enrolled subject." Sites are only required to send a signed consent form once; if the study involves multiple consent forms for this study, only a signed copy of the core consent form is required. Please note that if the site submits the correct version of the WIRB-approved consent form, but there are discrepancies in the signature lines (missing signatures, incorrectly completed signatures), WIRB staff will request an explanation from the site.

iv. Definition of Screen Failures and Withdrawals

Report the number of screen failures and withdrawals on the CRRF according to the following definitions. WIRB acknowledges that the definitions for these terms vary across the industry, but please apply the following definitions when reporting to WIRB:

Screen failure: subject removed from the study during the screening process because they did not meet all inclusion and exclusion criteria, or whatever other requirements must be met for research participation. Subjects who leave the study after randomization or assignment to study treatment should be counted as withdrawals rather than screen failures, even if the subject did not start the study treatment.

Withdrawal: Regardless of the reason for withdrawal, both subject-initiated decisions to withdraw and investigator- or sponsor- initiated withdrawals should be included in the reported number of withdrawals. Subjects who are withdrawn later in a study because they failed to meet study criteria for continued participation should be counted as withdrawals rather than screen failures. The majority of withdrawals take place after screening is completed.

v. Study Renewal

Sites receive a WIRB CRRF when the expiration date is approaching. The Board may conduct the study renewal review up to 30 days prior to the expiration date listed on the Certificate of Approval. **Review fees apply for the renewal service** and review is carried out unless WIRB receives a study closure notice *prior to the Board's renewal review.* If a closure notice is received by WIRB before the expiration date, but after the Board's renewal review, the site is still billed for the renewal review. To avoid unnecessary reviews and fees, do not delay reporting a study closure to WIRB if the expiration date is approaching. Please note that if you plan to close a study that is approaching its expiration date, no study activities may take place on the expiration date or following; therefore, if the study's expiration date is, for example, June 15, no study activities may take place on June 15 or following.

If the Board approves renewal for an additional review period, a Certificate of Approval is forwarded to the investigator and other study contacts as applicable. The Certificate of Approval states "Approval includes: Study and Investigator for an additional continuing review period. This approval expires on the date noted above." Approval of the study encompasses renewal of the protocol, all previously approved amendments or revisions, and the existing consent and study materials as previously approved.

If, at the time of renewal, the Board determines that a modification to the consent is necessary, the Certificate of Approval will indicate approval of a consent form and will be accompanied by a revised consent form (and a redline illustrating the Board's changes).

B. Study Closure

WIRB considers the study open at a site until a study closure report is received. A study closure report may be submitted when

1. all subjects have finished their final visits and follow-up **and**
2. for industry-sponsored research, the sponsor or the sponsor representative has indicated the study is closed at your site and
3. if the study was conducted under a Federalwide Assurance, all data analysis at the site is completed.

WIRB will close the study upon receipt of the closure report. A WIRB **Study Closure Report Form** is available at www.wirb.com.

WIRB sends closure confirmation notices to all study contacts upon receipt of a study closure form. Sites must have active on-going IRB approval in order to enroll subjects, perform any study interventions, collect/report new data, and/or, if under an FWA, analyze identified data at the site. If you receive a closure confirmation for a study you believe was closed in error, contact WIRB immediately to avoid a substantial gap in IRB oversight for the research.

To avoid unnecessary reviews and fees, do not delay reporting a study closure to WIRB if the expiration date is approaching.

C. Site Visits

Federal Regulations grant IRBs the authority to observe the consent process and the research (21 CFR 56.109(f); 45 CFR 46.109(e)).

WIRB conducts the following types of site visits:

- For-Cause – WIRB staff initiate "for-cause" site visits in response to concerns raised about the site, investigator, etc. These visits are usually carried out by WIRB Regional Representatives, Board members or WIRB management.
- Board-Directed – The Board directs site visits in response to concerns raised about the site, investigator, etc. These visits are usually carried out by WIRB Regional Representatives, Board members or WIRB management.
- Visits to Massachusetts Investigators – The Commonwealth of Massachusetts requires an on-site visit by a WIRB representative. Massachusetts investigators will be contacted to schedule a brief visit within a month of approval.

Sites receive a site visit confirmation notice soon after the site visit has been scheduled. The notice provides the time of the visit, the basis for the visit, and the agenda for the visit. For the fees associated with a WIRB site visit, please consult the current fee schedule.

The Board reviews all site visit reports. If any follow-up is required, the investigator will be informed about the Board's decision. WIRB does not release copies of site visit reports to sites or sponsors.

15. Fees

WIRB charges fees to cover the costs associated with the Board's review and the related administrative responsibilities. Fees do not influence the decisions of the Board, and the same fee is charged regardless of the action taken by Board (fees are not billed until the Board review has occurred).

A copy of our current fee schedule is available upon request from Client Services at 1-800-562-4789 or clientservices@wirb.com.

Research Review fees at WIRB fall into four general categories:

1. **Initial Review of the research**. Initial review encompasses the review of the research protocol, qualifications of the investigator, associated consent forms, protocol-related advertisements, questionnaires, screening scripts, and other submitted materials. The initial review fee funds the costs of the initial research review, as well as the costs of the ongoing review of unanticipated problems, and the monitoring of research progress for the first approval period.

   In addition to the initial review fee, additional fees may be charged if teleconference or videoconference with the site is necessary to complete the

initial review, if multiple consent forms are submitted, and if translation of consent forms and other subject materials is necessary.

Initial review of generic non-protocol related materials and exemption determinations are billed at a lesser rate than initial review of a protocol, consent form and investigator combination.

2. **Research Renewal Review fee.** In accordance with 45 CFR §46.109(e) and 21 CFR §56.109(f), IRBs must review ongoing research at least annually and that review must be substantive and at least comparable to the initial review. The protocol is reviewed on an annual basis, or more frequently as directed by the Board. The Board also examines each investigator's progress report and activities for the previous year, and if acceptable, grants approval for another period. The renewal review fee funds the costs of the Board's renewal review, as well as the costs of the ongoing review of promptly reportable information, for the additional year.

3. **Changes to Research**. Modifications to research which require board review, such as protocol amendments, revised protocols, updates to consent forms, and new recruitment or retention materials, incur a Change to Research fee, which covers the cost of reviewing the materials, and the related administrative responsibilities of preparing review documents and updating the investigator file at WIRB. The change in research fee applies each time board review and preparation of regulatory documentation is required for a research site. Changes that do not involve consent form review and preparation are billed at a lesser rate.

4. **Miscellaneous.** WIRB bills additional fees if videoconferencing or teleconferencing with the site is necessary in the course of the review process and if translations are requested.

Items disapproved by the Board can be reconsidered upon written request. The request must include a rationale for the reconsideration. There is no additional fee for the reconsideration. Reconsiderations of board-directed modifications do not incur additional fees if the requests concerns re-review of the **same language or item** originally reviewed by the Board. If new or alternate language is submitted, the Change to Research fee applies.

16. Reconsiderations

In accord with 21 CFR §56.109(e) and 45 CFR §46.109(d), WIRB notifies investigators in writing of the Board's decision to approve or disapprove proposed research activities, or of modifications required to secure approval. Disapproval notifications include a statement of the reasons for the Board's decision and offers opportunity to address the Board in writing or in person.

Requests for reconsiderations are given the same priority in scheduling as new review requests. The reconsideration will be reviewed by the panel that originally reviewed the request. There is no fee for the review. Requests for reconsideration and supporting materials may be directed to the WIRB contact identified in the letter conveying the Board's action and rationale.

If you disagree with the Board's re-consent instructions directed for a change in research, you may **promptly** contact WIRB and ask for a reconsideration; however, we advise you not to delay complying with the Board's instructions.

17. Other WIRB services

A. Clinical Pharmacology Unit Services

Clinical Pharmacology Unit Services
1019 39th Avenue SE Suite 120 | Puyallup, WA 98374-2115
Office: (360) 252-2467 | **Toll Free**:(866) 956-246 | **www.wirb.com**

In clinical pharmacology research reviews, timing is everything. The clock is always ticking for clinical pharmacology research. WIRB's Clinical Pharmacology Unit Services division is set up to respond quickly for a fast and thorough review. We have vast expertise with clinical pharmacology research, including Phase I, bioequivalence/bioavailability, diabetes, oncology, and renal research in healthy and diseased subjects.

With our clinical pharmacology review expertise, we have developed streamlined systems to meet almost any circumstance, while still placing the safety of our human subjects first.

Our Board is structured to be highly responsive, anticipating adaptive study design and addressing changes related to the safety and efficacy of the research.

During our pre-review site visits, we gather all critical information and ensure your site meets all safety standards, guaranteeing a faster review turnaround.

Our Board meets three times per week to provide accelerated turnaround times from completed submission to document delivery. From the time we receive your complete submission, our turnaround time is:

5–7 working days for initial reviews.
24–48 hours for deadline-driven material.

Your team will have a single point of contact who understands the unique needs of your organization, as well as time-saving online tools: All submissions and documentation are delivered electronically, and our secure portal, Connexus®

(https://connexus.wcgclinical.com/default.aspx), lets you submit and track your research review at any time.

WIRB has a global network and decades of experience working around the world. In international reviews, our panel observes strict compliance with local and regional regulations, as well as cultural sensitivities, so you can be sure your study will pass the strictest scrutiny, anywhere in the world.

Nationally and internationally, you will have a local coordinator who will provide guidance and represent you to the Board. Our local coordinators are authorities in process submission, and specially trained as subject matter experts (SMEs) in their area.

WIRB's staff of experts and educators offers a wide array of education, consulting, and staffing services for investigators, local IRBs, and sponsors. WIRB can help you write your protocol or your consent form, and provide regulatory support for local IRBs.

To prepare your submission, please review the relevant industry regulations, view WIRB's submission resources, or contact us with questions. When you are ready to submit, log on to Connexus®(https://connexus.wcgclinical.com/default.aspx).

B. Biosafety review

Biologics raise new issues

Institutional Biosafety Committee Services
PMB 2436, 2103 Harrison Avenue NW | Olympia, WA 98502-2607
Office: (360) 252-2850 | **Fax**: (360) 252-2820

Safe storage, handling, and disposal of gene-modified, biohazardous materials—these issues are among the many challenges for investigators and sponsors of research involving recombinant DNA. WIRB's IBC services can help your team navigate this complicated environment and protect the safety of staff, communities, and the environment.

More IBC experience
With WIRB, you will have the most experienced IBC partner out there. Since 2000, we have evaluated more than 175 human gene transfer protocols—probably more than any organization outside the FDA and NIH.

Your own local IBC
We set up and operate your institution's local IBC to comply with NIH Guidelines for Research Involving Recombinant DNA Molecules. The IBC roster brings together prominent and experienced biosafety experts from around the country, with local

members representing the institution and the surrounding community.

International IBCs
We can also help set up local IBCs outside the U.S. Our IBC Services group has successfully operated IBCs in eight countries in Africa, South America, Central America, the Caribbean, Europe, and Canada. If the study institution or sponsor receives U.S NIH funding for rDNA research, then the review must meet NIH requirements.

Education and consulting for IBCs
According to NIH Guidelines, institutions conducting rDNA research must assure appropriate training for IBC members. Our expert staff can help with training, establishment of standard operating procedures, review of national regulations, and other biosafety challenges. **Getting started**
To learn more and discuss your IBCS needs, contact us.
Institutional Biosafety Committee Services (IBCS)
Mail Stop: IBCS
1019 39th Avenue SE Suite 120
Puyallup, WA 98374-2115
Phone: (360) 252-2850 or (800) 562-4789 Ext. 2850
Fax: (360) 252-2820
E-mail: ibcs@wirb.com

C. Consultations

Education & Consulting Services
a division of WIRB

Education and Consulting Services
1019 39th Avenue SE | Puyallup, WA 98374
Office: (360) 252-2500 | **Fax**: (360) 252-2498 | **www.wirb.com**

Protocol review and development
Catch problems before submission—let us help write your protocol or review your existing protocol to see if there are any regulatory or ethical issues that might prevent or delay IRB approval.

Consent form review and writing
WIRB's experts can write your consent form or review your existing consent form to be sure it is understandable and in compliance with regulations and applicable law.

Onsite compliance assessment for researchers
Have an expert visit your site for a consultation on best practices and assessment of compliance with regulations and other applicable law, including a review of SOPs, delegation procedures, recruitment, and consent process. If issues are identified we can help you develop and implement a corrective action plan.

Consultation services for IRBs

WIRB has experienced IRB professionals with a wealth of knowledge to provide assistance to IRBs who are facing challenges and require expertise. We have Certified IRB Professionals who can offer sound and valuable solutions to the issues that face your IRB.

Onsite compliance assessment for IRBs
WIRB's experts will evaluate your operations and provide a report and suggest best practices. We will talk with your staff and board members and review written policies and procedures, IRB minutes, and selected study files to see if the documentation is adequate and to see if your reviews are consistent with regulations, guidance, and SOPs. Following our assessment, we will conduct a gap analysis and provide information on practices.

Support for IRB review
WIRB can provide interim or permanent regulatory support for IRB review. We can advise your IRB before, during, and after the review to ensure that the required determinations are made and documented, and that the review is in compliance with regulations, guidance, and local law.

Data and safety monitoring consultations
We can provide protocol development consultation to focus your data monitoring plan and help present it to regulators.

Accreditation Support
We can help you navigate the accreditation process from start to finish, including self-assessment, development of documentation that satisfies AAHRPP's Standards and Elements, the application process, and response to AAHRPP reports.

Getting Started
For more information on WIRB's consultation offerings, contact us and check us out on the web at http://wcgirb.com/about.html.

D. Exemption Determinations

Occasionally investigators need a formal IRB determination that research is exempt under 45 CFR 46.101(b) for the purpose of obtaining federal funding, or for meeting the submission requirements of medical journals. WIRB will provide formal exemption determinations for research under 45 CFR 46.101(b) for a fee. WIRB will also provide exemption determinations from the FDA regulations (21 CFR Parts 50, 56, 312 and 812) for those exemptions allowed under 21 CFR 56.104. However, WIRB generally does not provide determinations on whether a given research study meets the definition of a “clinical investigation” or a “marketing application,” because determination of these definitions involves the sponsor’s intent as to whether or not to submit data to FDA, which WIRB cannot independently determine.

Use the Request for Exemption Determination form available on the Download Forms page of www.wirb.com to request an exemption determination (US and Canadian versions available).

18. FAQs

Are we required to obtain the consent of subjects who were originally enrolled as children, but have now reached the age where they can consent for themselves?
Yes. Unless consent has been waived, WIRB requires you to obtain the consent of subjects who reach the age of majority during the research. You may use the current WIRB-approved consent form to obtain their consent, or, if the approved consent form is not appropriate for doing so, you may download the consent addendum and present it, along with the current WIRB approved consent form, to the subject in order to obtain his/her consent.

If you use the addendum available on our web site (http://www.wirb.com/Documents/Minors_to_Adults_Addendum.doc), please remove the statement from it regarding authorization to use and disclose information if the consent form signed by the parent/guardian did not include an authorization section.

You do not have to seek WIRB approval of the generic addendum before using it if you use it without alteration (besides removal of the authorization statement if appropriate as outlined above).

Can I make changes to an advertisement without resubmitting to WIRB?
Changes made to an advertisement may alter the effect of the advertisement on potential subjects (changes to pictures, font sizes, font types, etc.) WIRB must review anything that could alter the impact of what was previously reviewed, as required in 21 CFR 56.108(a)(4).

Contact Client Services via e-mail at clientservices@wirb.com or call 1-800-562-4789 for more information about modifications to approved recruitment materials.

Can I submit a hand-written submission form?
WIRB does not accept hand-written initial review submission forms. Hand-written submissions can result in significant delays and miscommunications. You may contact Client Services at 1-800-562-4789 or ClientServices@wirb.com for help using the electronic copies of the submission form.

Can I submit paperwork before choosing a PI?
Yes. WIRB can assist sponsors and CROs during the planning stages of a multi-center study by pre-reviewing the protocol and subject materials, including the consent form. Log on to via Connexus® (https://connexus.wcgclinical.com/default.aspx) or click on Download Forms to complete the *Initial Review Submission Form for Sponsors and CROs* to request a pre-review (please note that effective December 21, 2015, that form

will be retired replaced with a general purpose Initial Review Smart Form available on the WIRB website). The fee for initial review applies.

Can WIRB do the IRB and IBC reviews on my clinical trial?
Yes. WIRB can review research involving recombinant DNA for human subject protection (IRB services), researcher, staff, and environmental protection (IBC services), or both.

Does my study require a Certificate of Confidentiality, and if so, how do I obtain one?
WIRB's Board requires a Certificate of Confidentiality (CoC) for certain types of research in order to provide the subjects with extra protection of their confidential information as defined in 45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7). The determination to require a CoC is based on whether the research involves a subject population that might be prone to face legal or social harm by another's discovery of private, confidential, or protected information, such as:

- illegal behavior (e.g., crime, quasi-crime, supervision violation, contempt, child abuse, domestic violence, etc.);
- illegal status (e.g., alien, child runaway, AWOL);
- stigmatized behavior and/or diseases (e.g., HIV, alcoholism, drug abuse, mental illness);
- embarrassing behavior (e.g., immoral behavior, sexual behavior);
- discriminatory condition (e.g., employability, reputation, financial standing).

Listed below are links to helpful pages on the Office for Human Research Protection (OHRP) website and the National Institutes of Health (NIH) website. The pages provide information about acquiring a Certificate of Confidentiality.

- http://grants2.nih.gov/grants/policy/coc/
- http://grants.nih.gov/grants/policy/coc/contacts.htm
- http://www.hhs.gov/ohrp/policy/certconf.html

Does WIRB provide services internationally?
Yes. With experience in more than 70 countries, we can help you meet all the logistical, cultural, and regulatory challenges of international research. We reference local laws, customs, and attitudes to ensure that research is culturally and legally acceptable.

How do I collect data on partners of subjects who become pregnant?
Many protocols now include instructions for investigators to collect data on the outcome of pregnancies that occur in partners of male subjects. WIRB follows 45 CFR 46, which defines research as use of private, identifiable information for research purposes. Because investigators would be obtaining private information from the pregnant partner and infant, the partner would be a subject in the research. Investigators must obtain consent from the pregnant partner before any data collection can occur, and WIRB requires a consent form to be submitted for these subjects if a pregnancy occurs. If plans for obtaining consent from the pregnant partner (or a request for a consent

waiver) are not submitted at initial review, the Board may approve the research, but add a note to the Certificate of Approval reminding the investigator and sponsor that pregnant partners and their infants cannot be followed up on until WIRB approves a consent plan for them (some sites may receive a letter rather than the note on the COA). Please note that no action is necessary until such time as a pregnancy occurs.

A template consent form is available on the Download Forms page of www.wirb.com. The template consent form cannot be used without WIRB approval.

How do I consent a cognitively impaired subject?
First check to be sure the protocol and WIRB allow enrollment of cognitively impaired subjects in the research – there are special criteria for enrollment of this vulnerable group in research. If enrollment of them is allowed by the protocol and no prohibition on their enrollment was provided by WIRB, WIRB expects that consent will be obtained from a legally authorized representative (LAR), and that the assent of the subject will be obtained to the extent compatible with their capacity.

FDA regulation 21 CFR § 50.20 and HHS regulation 45 CFR 46.116 state that:
No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

If an adult subject is not medically capable and/or legally competent to consent to participate in a study, the federal regulations require that a legally authorized representative consent for the subject. The definition of "legally authorized representative," as described in FDA 21 CFR § 50.3 and HHS 45 CFR 102(c) is:

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

The applicable law is the law of the state, as well as any other local law. Thus, the definition of "legally authorized representative" will be determined by state law or other local law. If a subject is medically incapable and/or legally incompetent, then a legally authorized representative, as determined under state or local law, must consent on the subject's behalf. The Office for Human Research Protections (OHRP) has determined that state laws addressing consent for treatment decisions concerning the same procedures involved in the research are an acceptable basis for determining who may serve as a "legally authorized representative."
For questions regarding the legal status of an individual subject and the applicability of local law to an individual subject's enrollment in research, contact a healthcare attorney admitted to the bar in that state. Sites should be aware that changes in statutes and regulations occur frequently, and that court decisions may determine or change the interpretation of such statutes and regulations. Legal counsel should always be consulted to determine the current state of applicable law.

The PI is unexpectedly no longer able to oversee the study. What do I do?

WIRB must be assured that the investigator can personally oversee the conduct of the research and the protection of human subjects [21 CFR 56.102 (h); for Canadian investigators: Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations (if applicable), Medical Devices Regulations (if applicable)].

As soon as possible, WIRB will need either a study closure request from the site, or a submission of a new PI for the Board's review.

WIRB normally requires a letter of relinquishment from the old PI, but if a letter is not available, provide the following information in its place:

1. When did the PI leave this study?
2. Why did the PI leave this study?
3. Who has provided oversight in the PI's absence?
4. Have there been any subject safety concerns during the PI's absence?

How does WIRB handle the requirement for clinicaltrials.gov text in consent forms?

As of March 7, 2012, consent forms for certain types of research must include a new element. Federal regulation 21 CFR 50.25(c) states:

> "When seeking informed consent for applicable clinical trials, as defined in 42 U.S.C. 282(j)(1)(A), the following statement shall be provided to each clinical trial subject in informed consent documents and processes. This will notify the clinical trial subject that clinical trial information has been or will be submitted for inclusion in the clinical trial registry databank under paragraph (j) of section 402 of the Public Health Service Act. The statement is: "**A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.**"

How do I create a Connexus® account?

Go to **Connexus** (https://connexus.wcgclinical.com/default.aspx) and click "Register Me".

How do I obtain informed consent from someone who speaks and understands English, but cannot read English?

Sometimes potential subjects speak and understand English, but cannot read due to blindness, illiteracy, or some other reason. These individuals may still participate in a research study as long as the protocol has not excluded limited or non-readers and there is an impartial witness present for the consent process, in accordance with ICH 4.8.9, which states:

ICH 4.8.9 - If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written

information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative and that informed consent was freely given by the subject or the subject's legally acceptable representative.

The definition of impartial witness is provided at ICH 1.26, which states:
ICH 1.26 Impartial Witness - A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Unless consent has been waived or the protocol excludes enrollment of limited readers or non-readers, involve an impartial witness in the consent process when enrolling limited or non-readers and document the participation of the impartial witness using the designated signature lines on the WIRB-approved consent form. In the absence of designated signature lines, download the WIRB standard impartial witness form from www.wirb.com.

The impartial witness block may not be used to enroll subjects who speak a language other than English. WIRB requires that non-English speaking subjects sign a translated consent form. See the frequently asked question "How is consent obtained from a non-English speaking subject?" for more information.

How do I submit a change of Principal Investigator (PI)?
WIRB requires written authorization of the change from several parties:

- Please provide confirmation from the sponsor that the change is acceptable and has been approved. The sponsor is required to select investigators under 21 CFR 312.53(a).
- Provide a letter from the current PI, relinquishing responsibility for the study (if a letter is unavailable, please indicate that it is not available and why). WIRB expects departing PIs to arrange for an orderly transition of their research to the new investigator and we are hesitant to authorize a change of oversight without acknowledgement of the change from the current investigator.

In addition to the letters described above authorizing the change, the request should also be accompanied by:

- A WIRB initial review submission form completed by the new PI;
- Documentation of the new investigator's qualifications to conduct the study (a CV and, when applicable, a professional license); and

- A request to update the investigator information in the existing consent documents to reflect the new investigator information.

How does WIRB handle initial review of consent forms from affiliated institutions?

Multi-site protocols previously approved by WIRB:

If WIRB has previously approved the protocol, WIRB will be able to generate a consent form for you based on the previously approved consent form and site-specific information and institution-specific requirements. If so, you do not have to submit a consent form. You may log into Connexus (https://connexus.wcgclinical.com/default.aspx) to preview the consent form currently approved by WIRB for the research.

If your institution has language that is chosen by a checklist or other documentation such as cover letters or grants and contracts forms, it must be included with the application to WIRB as usual. WIRB will incorporate this language into the consent form that will be approved for you.

If your institution requires protocol-specific insertion of language to the text of the consent form, such as study visit durations or a listing of which procedures are standard care, clearly mark those changes on a copy of the WIRB-approved consent form [log into Connexus (https://connexus.wcgclinical.com/default.aspx) to preview the consent form currently approved by WIRB for the research]. All other standard institution language will be incorporated by WIRB and does not need to be marked on the submitted consent form.

Multi-site protocols NOT previously approved by WIRB:

If WIRB has not previously approved the protocol, submit the sponsor's template as a Microsoft Word compatible file (please contact Client Services if you need assistance with submitting in this format). There is no need to incorporate any institution-required language because WIRB will do so as part of its review, including information from the submission form and any language from a checklist or other documentation such as cover letters or grants and contracts forms.

If your institution requires protocol-specific insertion of language to the text of the consent form, such as study visit durations or a listing of which procedures are standard care, clearly mark those changes on the sponsor's template in Microsoft Word compatible format.

Single-site protocols:

Submit a consent form as a Microsoft Word compatible file that will be reviewed as new. Please make sure you have reviewed the information on this website on consent forms. You may also request to have WIRB write the consent form (extra fee applies). Please

incorporate your institution-required language into the submitted consent form. Please contact your institutional department for the latest version of required language.

How is consent obtained from a non-English speaking subject?
WIRB requires that non-English speaking subjects sign a WIRB-approved translated consent form. WIRB's Translations staff can arrange to have a WIRB-approved consent form or subject material translated into any language, or the site/sponsor can submit to WIRB a translated document along with a signed translator certification statement for verification and approval. Specific submission requirements may be obtained from the WIRB Translations staff.

You must also explain your plans for 1) conducting the consent discussion in the language understandable to the subject, and for 2) ongoing communication with the subject throughout the research and in case of emergency. For example, your site might indicate "At least one member of the research team is fluent in the language that will be used for communication, and that research staff member(s) will be available during emergencies," "The research team has 24-hour access to a translation service with sufficient medical expertise to discuss the research in this study," or provide another appropriate plan.

Please provide these plans each time you request a translation into a new language for a particular study. Your translation requests may be delayed if you have not already provided an acceptable language-specific and research-specific plan.

If a site has an unexpected need to for a translated consent form, WIRB has adopted the following policy regarding the use of a short form consent process to enroll subjects who do not speak English. This policy is limited to the situation when **both** of the following are true:

- A full-length version of the consent form in a language understandable to the subject is not available, and
- It is in the subject's best medical interest to be enrolled in the research before a translated consent form can be obtained.

The short form will follow the OHRP template short form[2], and the subject will have to be reconsented within 30 days with a WIRB-approved consent form in a language understandable to the subject.

Each of the following steps must be followed:

1. The Principal Investigator is to insert study specific information, including title of study, principal investigator, and contact information into the OHRP template short form.
2. The subject must be given a copy of the short form in the language understandable to him/her to read;
3. A translator/interpreter must orally present the entire IRB-approved English ICF;

[2] Online at http://www.hhs.gov/ohrp/policy/ic-non-e.html#sample

4. The consent process must be witnessed by an individual who is fluent in both English and the subject's language;
5. The English ICF must be signed by the investigator and the witness;
6. The short form must be signed by the subject, investigator, and witness;
7. The subject must be given signed copies of the English ICF and short form;
8. The original signed English ICF and the original signed short form should be retained in the subject's research record and medical record, if appropriate; AND
9. The PI will then obtain a fully translated version of the consent form at the earliest opportunity. The subject would then be re-consented using the translated consent form within 30 days.

How should consent forms be submitted?
Consent forms should be submitted in a Microsoft Word compatible format. This includes files with extensions .doc (Word 2003 and earlier), .docx (Word 2007 and later), and .rtf (Rich Text Format, available in most word processing programs). If you have received only a .pdf version from the sponsor, please attempt to get a Word version; WIRB maintains consent forms in Word format and conversion from pdf to Word can introduce errors. We encourage sites to check Connexus (https://connexus.wcgclinical.com/default.aspx) for the current approved consent form when putting together a request for review; the current protocol-level and site-specific consent form are posted and available for download. Contact Client Services if you need any assistance with submitting your documents in this format.

How will I be notified of my ad's approval?
Advertisements are approved in one of two ways: "As Submitted" (no changes) or "As Modified." Board-directed changes are indicated on the ad returned with the certificate of approval.

Ads submitted with the protocol and consent form at the time of initial review will be reviewed with the initial approval packet. Approved ad(s) will be listed on the certificate of approval, and show any changes required by WIRB.

WIRB does not routinely apply approval stamps to approved advertisements The Certificate of Approval listing approval of the ad is documentation of WIRB's review and approval of the advertisement.

How will I receive documents from WIRB?
Your approval documents will be posted on WIRB's secure online site (Connexus -- https://connexus.wcgclinical.com/default.aspx), and you will receive an e-mail with a link to the documents when they have been posted. Contact WIRB Client Services to request a change to the delivery method.

You can also access your approval documents and other research-related information 24 hours a day via WIRB's web portal Connexus

(https://connexus.wcgclinical.com/default.aspx). Click “Register Me” to set up an account.

If there is another IRB involved in my research, what are the options available for WIRB involvement in the oversight?
WIRB can engage in an agreement with another IRB to:

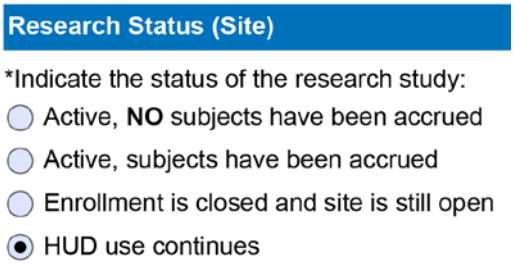
- Provide complete dual oversight of research with another IRB, in which both IRBs provide initial and continuing review of all aspects of the research;
- Provide split dual oversight of the research with another IRB, in which WIRB provides IRB oversight for specific physical locations, and an institutional IRB provides IRB oversight of the aspects of the study conducted at the institution; or
- Assume jurisdiction from an existing institutional IRB for the review of a study or studies.

Is my protocol exempt from review?
Upon request, WIRB will provide a written opinion that a proposed project is exempt from the requirement for IRB review or that it does not require IRB review because the project does not involve research or does not involve human subjects. Complete the Request for Exemption Determination form.

My HUD is not research; how do I fill out the WIRB Continuing Review Report Form?
Humanitarian Use Devices (HUDs) are approved devices whose use must comply with 21 CFR 814, Subpart H “Humanitarian Use Devices,” and 21 CFR Part 803, “Medical Device Reporting.” Federal regulation 21 CFR 814.124 requires IRB review and approval of use of the device.

WIRB requires all approved, active sites to provide progress reports at least annually (21 CFR § 56.109(f)). Continuing Review Report Forms are sent to sites approximately two weeks before their due date.

Starting in January 2016, the Continuing Review Report Forms sent out by WIRB will include an option for HUD users to indicate the form is for reports of HUD use:



In situations where progress reports are not returned with accurate information in a timely manner, federal regulations grant the Board authority to suspend or terminate approval of the use of the device at the site (21 CFR § 56.113).

If the Board takes action to suspend approval for use of a HUD at your site, you would not be allowed to use the HUD on any new patients until the Board receives the information it requires and votes to lift the suspension.

Therefore, it is imperative that you submit the accurate and complete continuing review reports by the due date stated on the form.

The FDA guidance on Humanitarian Use Devices is available here: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110194.htm

My site is in California, but the contents of the California Experimental Subjects' Bill of Rights don't apply to my research project. Can I ask WIRB to omit the Bill from my approved consent form?

Yes, WIRB will consider omitting the Bill from your approved consent form. Sites that believe the Bill is not applicable to their research and that desire to see it omitted from their consent form can submit a change in research request. WIRB review fees apply for requests submitted as changes in research.

As of June 1, 2010, the California Experimental Subject's Bill of Rights is not included in the approved consent form. However, consent forms continue to contain a reference to it ("If you agree to be in this study, you will receive a signed and dated copy of this consent form and the Experimental Subject's Bill of Rights for your records"), and it continues to be provided to California sites with the Initial Review approval documents.

The text of the applicable California law can be found in the California Health and Safety code, section 24174.

Should I do anything differently if I am submitting audio and/or video recordings?
To avoid costly re-work, audio or video recordings should be submitted first as a script. When the script is approved by WIRB, it may then be used to make the final recording. The recording should then be submitted with a copy of the WIRB approved script for final review as a video tape, audio tape, CD, DVD, Windows Media file (.wmv), etc. **The submitted audio or video recording is kept in the WIRB files (to comply with federal recordkeeping regulations for IRBs); the recording is NOT returned to the site. Please be sure to retain a copy for use.**

What are WIRB's requirements for consent form signatures?
1. Subject Signatures The subject must sign and date the consent form [21 CFR 50.27(a); 45 CFR 46.117(a), ICH 4.8.8].

WIRB may waive this requirement, when appropriate, under 21 CFR 56.109(c) or 45 CFR 46.117(c)(2), or when consent is entirely waived under 21 CFR 50.23, 21 CFR 50.24, or 45 CFR 46.116(d). Please see the WIRB FAQ on the Waiver of Documentation of Consent and Waiver of Consent. For requests for waiver of consent, and if you are a covered entity under HIPAA, please complete Request for Full Waiver Authorization Under HIPAA.

2. Signature of Person Who Conducted the Informed Consent Discussion: The person who conducts the informed consent discussion must sign and date the consent form (ICH 4.8.8).

3. Witness Signature: WIRB does not require a witness signature on the consent form, except in rare cases or as required by state or local law. However, WIRB will include a witness signature block at the request of the investigator or the sponsor. Because WIRB does not require a witness signature, WIRB does not have written procedures identifying who may serve as a witness. The investigator or the sponsor should have written procedures describing who may be a witness and what the witness signature signifies. If a witness signature block is included on the consent form, it must be signed for each consent form, unless the investigator or sponsor written procedures allow otherwise.

4. Signature of Impartial Witness: If a subject or a legally authorized representative (LAR) is unable to read because of blindness, illiteracy, or some other reason, an impartial witness should be present during the entire consent process, and should sign and date the consent form in compliance with ICH E6 4.8.9. The definition of an impartial witness is provided at ICH E6 1.26. An impartial witness's signature may not be used to attest to ad hoc translation of the consent into a language different than the language in which the consent form is written.

The impartial witness signature block should be left unsigned unless there is an impartial witness present for the consent process. Please see the frequently asked question, "How do I obtain informed consent from someone who speaks and understands English, but cannot read English?" for further discussion of the impartial witness requirements.

What if changes are desired in sponsor-approved language in a consent form?

Initial Review:
To request that WIRB consider at the time of initial review wording that differs from the sponsor's template consent form or the consent form already approved by WIRB (approved during WIRB's pre-review or approved for other sites), you have two options: 1) You may rewrite all or some of the consent form yourself and submit the changes clearly marked on the WIRB-approved copy of the consent form (or on the sponsor's template if no WIRB-approved version exists); or 2) You may send a cover letter communicating your concerns, and it will be used in the WIRB review and editing of the consent form.

After Initial Review:
To request changes to consent forms for approved research, WIRB requires a completed *Change in Research Submission Form* and either a copy of the current WIRB-approved consent form with proposed changes clearly marked, or the changes can be detailed in a document specifying the requested changes.

Proposed new changes may be submitted either on a copy of the current WIRB-approved consent form with new changes tracked in redlined format or handwritten on the form, OR the changes can be detailed in a document that indicates each change and the section of the consent form where the change should be made.

For more information on submitting consent form changes, please contact Client Services via e-mail at ClientServices@wirb.com or by calling 1-800-562-4789.

Where do I find re-consent instructions?
WIRB's Certificate of Approval (COA) provides re-consent instructions under the area titled **WIRB APPROVAL IS GRANTED SUBJECT TO**.

What if I disagree with the Board's re-consent instructions?
If you disagree with the Board's re-consent instructions, you may PROMPTLY contact WIRB and ask for a reconsideration; however, we advise you not to delay complying with the Board's instructions.

What if I received two changes to the consent form recently and each accompanying Certificate of Approval provided different re-consenting instructions?
The Board expects you to apply the more strict of the two sets of instructions. For example, if the first consent form change included updated risk information and was accompanied by instructions to re-consent all subjects, and the subsequent consent form change was the addition of a new site and the Board directed that the revised consent form only be presented to new subjects, the site is still expected to provide the updated risk information to all subjects using the most current version of the consent form.

What if the Board didn't require all subjects be re-consented, but the site would like to re-consent all subjects?
If the site is not required by the Board to re-consent all subjects, the site is still free to do so.

What information is required when submitting advertisements to WIRB for review?
The WIRB Change in Research Submission Form should be used to submit recruitment materials for review after initial review of the research. The basic information required includes: investigator name, sponsor name, research protocol number, and the name of the person submitting. Ads must be submitted and approved by WIRB before they are used.

For best results, when submitting subject recruitment materials or other subject materials (diaries, questionnaires, etc.) that have been previously reviewed by WIRB, state in the cover letter which items have been previously reviewed by WIRB. WIRB support staff will provide the Board with information about the previous Board review, and the previous decision of the Board will be taken into account when the additional materials are reviewed.

If some recruitment will be done on a website, submit the recruitment portions of the website for WIRB review; do not submit the portions of the website that are not intended for subject recruitment.

Ads can be submitted via Connexus (https://connexus.wcgclinical.com/default.aspx) by sending e-mail to ClientServices@wirb.com, or via postal mail or fax.

WIRB requires a copy of print ads as they will appear, to allow the Board to review the font size, font style, images, etc.

Advertisements that will be used by some or all participating investigators should be identified as such in the cover letter or submission form. Identifying shared advertisements as such will help ensure consistent review of ad materials for all participating sites.

Click here for additional guidelines regarding subject recruitment materials submitted to WIRB.

What information will WIRB need regarding the study staff, sub-investigators, and the sites?

WIRB will need the name and title of each person involved in the conduct of the research (those members of the study team who have contact with subjects or distribute study articles), a description of the role of each study member, and a curriculum vitae for each sub-investigator. WIRB's initial review submission forms provide a space for sites to list the names, titles, and duties of the study staff.

WIRB must be assured that the investigator can personally oversee the conduct of the research and the protection of human subjects. 21 CFR 50.3(d).

WIRB will need to know the number of sub-investigators. Possible relevant information includes whether the PI holds periodic meetings, whether all of the sub-investigators are on rotation at a clinic, whether multiple specialties are represented, and if written procedures exist for the conduct of research.

WIRB will need to know some basic information about each location where the research will take place. The initial review submission form solicits this information about the sites. Approved locations are listed on the Certificate of Approval.

What is a clinical trial?

The commonly used terms "research trial" and "clinical trial" generally refer to the overall research project at one or more investigator sites. WIRB does not use "trial" in consent forms because of possible misunderstanding by a lay reader.

What is a legally authorized representative (LAR)?
FDA regulation 21 CFR § 50.20 and HHS regulation 45 CFR 46.116 state that:
No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

If an adult subject is not medically capable and/or legally competent to consent to participate in a study, the federal regulations require that a legally authorized representative consent for the subject. The definition of "legally authorized representative," as described in FDA 21 CFR § 50.3 and HHS 45 CFR 102(c) is:

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

The applicable law is the law of the state, as well as any other local law. Thus, the definition of "legally authorized representative" will be determined by state law or other local law. If a subject is medically incapable and/or legally incompetent, then a legally authorized representative, as determined under state or local law, must consent on the subject's behalf. The Office for Human Research Protections (OHRP) has determined that state laws addressing consent for treatment decisions concerning the same procedures involved in the research are an acceptable basis for determining who may serve as a "legally authorized representative."

For questions regarding the legal status of an individual subject and the applicability of local law to an individual subject's enrollment in research, contact a healthcare attorney admitted to the bar in that state. Sites should be aware that changes in statutes and regulations occur frequently, and that court decisions may determine or change the interpretation of such statutes and regulations. Legal counsel should always be consulted to determine the current state of applicable law.

What is a Principal Investigator (PI)?
The PI is the named person who is responsible, under the regulations, for conduct of the research. WIRB prefers that only one investigator be named for this responsibility (Principal Investigator), but will allow a second person upon request (Co-Principal Investigator). Please note that federal regulations do not recognize Co-Principal Investigators; therefore, the Board approves the two investigators as if each is THE investigator and holds each individually responsible for the conduct of the entire study. Canadian regulations do not allow Co-Principal Investigators in this sense at all.

If there are multiple sub-investigators and/or sites, WIRB may require an explanation as

to how the PI will personally conduct or oversee the research, as required under 21 CFR 50.3(d), 21 CFR 312.60, and Box 9 of the FDA Form 1572.

What is a Sub-Investigator?
In parallel with the FDA's definition of a sub-investigator (21 CFR 312.3(b)), WIRB considers a sub-investigator to be any team member, other than an investigator, who may help in the design and conduct of the investigation, but does not actually directs its conduct.

The FDA provides further detailed guidance on this topic in their guidance document titled "Frequently Asked Questions – Statement of Investigator (Form FDA 1572)" available here:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf.

What is a protocol?
The "protocol" is the written, detailed description of the research project.

What is a research study?
The term "study" is used by WIRB to mean the combination of a particular research protocol and investigator.

What is a sponsor?
A sponsor is the company, person, agency, or other party that designs the research, typically funds the research, and bears the sponsor responsibilities under the regulations, but does not actually conduct the investigation ("sponsor-investigators" are an exception).

What is a waiver of consent and what criteria must my study meet if I request one?
For FDA regulated studies, waiver of consent must meet requirements of either 21 CFR 50.23 (a) - (c) (waiver of consent for individual emergency use) or 21 CFR 50.24 (emergency research without consent), or FDA guidance issued 04-25-2006 for In Vitro Diagnostic Device Study Using Leftover Human Specimens That Are Not Individually Identifiable.

For individual emergency waivers of consent, prospective IRB approval is not always necessary if a patient's life can be saved. See the FAQ below titled "What is the difference between "Emergency Use" and "Treatment Use," and how do I determine which situation I have?" for more information, or refer to 21 CFR 50.23 (a)-(c).

If you are requesting a waiver of consent and the research is not an FDA regulated study, then criteria from 45 CFR 46.116(d) must be met. WIRB applies this standard to all requests for waiver of consent for non-FDA regulated research.

- The research involves no more than minimal risk to the subjects.
- The waiver or alteration will not adversely affect the rights and welfare of the subjects.

- The research could not practicably be carried out without the waiver or alteration.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

If you are a covered entity under HIPAA, please complete the WIRB form *Request for Full Waiver Authorization Under HIPAA.*

What is a waiver of documentation of consent and what criteria must my study meet if I request one?
A waiver of documentation of consent is a waiver of the requirement for a signature on a consent form. The regulations allow the Board to approve this type of waiver if:

- The research is of minimal risk and involves no procedures for which written consent is usually required; or
- The only record linking the subject and the research would be the consent document and the principal risk of the research is the risk of breach of confidentiality.

Subjects enrolling in a study under this type of waiver must be provided with the elements of consent required by the regulations and subjects must consent to participate.

The Board will need to review the information that is provided to subjects to obtain consent to ensure that the required elements of consent are included in the consent discussion. Investigators requesting a waiver of documentation of consent must submit a written statement or script of this information for the Board's review. A template "Information Sheet" is available on the Download Forms page.

What is the difference between "Emergency Use" and "Treatment Use," and how do I determine which situation I have?
"Emergency Use" means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and where there is not sufficient time to obtain IRB approval, as stated in 21 CFR 56.102(d). Life-threatening, for the purposes of section 21 CFR 56.102(d), includes both life-threatening and severely debilitating conditions, as defined below:

- Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted, and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand, or foot, loss of hearing, paralysis, or stroke.

“Treatment Use” is described in the regulations (21 CFR 312.34) as follows: “During the clinical investigation of the drug, it may be appropriate to use the drug in the treatment of patients not in the clinical trials, in accordance with a treatment protocol or treatment IND. The purpose of this section is to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development process as possible, before general marketing begins, and to obtain additional data on the drug’s safety and effectiveness…. Treatment use of an investigational drug is conditioned on the sponsor and investigators complying with the safeguards of the IND process, including the regulations governing informed consent (21 CFR part 50) and institutional review boards (21 CFR part 56) and the applicable provisions of part 312, including distribution of the drug through qualified experts, maintenance of adequate manufacturing facilities, and submission of IND safety reports.”

Please Note: Regulations require that an emergency use of a test article be reported to the IRB within five working days (21 CFR 56.104(c)). Consequently, you must report an emergency use to WIRB within five working days of its occurrence, even if you communicated with WIRB prior to the emergency use. You may use the form posted here to report the use to WIRB.

If you are considering treatment use, see the FDA draft guidance “Individual Patient Expanded Access Applications: Form FDA 3926”. In addition to providing an overview of the FDA policy in regard to expanded access (treatment use), the draft guidance introduces and describes draft Form FDA 3926 (Individual Patient Expanded Access—Investigational New Drug Application (IND)).

What is WIRB's policy regarding the Statement of Investigator, form FDA 1572?
Investigators are not required to submit a 1572 to WIRB, even when one is required by the FDA for the research being conducted. The FDA Information Sheet "Frequently Asked Questions - Statement of Investigator (Form FDA 1572)" defines the 1572 as: An agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.

The same information sheet goes on to explain that:

The 1572 has two purposes: 1) to provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the clinical investigation, and 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations.

For questions regarding completion of and requirements for a 1572, sites may refer to the guidance issued by FDA here: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf.

What is WIRB's position on placebo-controlled studies?
Click here to view the checklist WIRB uses to review placebo-controlled studies in .pdf format or Microsoft Word format. This checklist is fully discussed in the article "Ethical Concerns in Placebo-Controlled Studies: An Analytical Approach."

The article was published in the Drug Information Journal, Volume 36, Number 2, 2002.

What makes WIRB a unique, world-class IRB?
WIRB is the only independent IRB that delivers IRB, IBC, DSM and Education and Consulting services as well as international reviews to its clients. Additionally, in partnership with the World Health Organization, WIRB offers the International Fellows Program to ensure international observance of human subject protection ethics around the world.

When submitting items to WIRB for review, is the use of the submission form required?
Yes, submission forms are required for initial review and for change of principal investigator requests. They are also recommended for submissions of changes in research, and subject recruitment requests. Click "Download Forms" on www.wirb.com to download access your desired form.

If you need help with any of the WIRB submission forms, please contact Client Services via e-mail at ClientServices@wirb.com or by calling 1-800-562-4789.

If an affiliated institution requires protocol-specific insertion of language into the text of the consent form, such as study visit durations or a listing of which procedures are standard care, submit a copy of the WIRB-approved consent form with those changes clearly indicated . All other standard institution language will be incorporated by WIRB and does not need to be indicated on a submitted consent form – deviations must be approved by the institution.

Consent forms must be submitted as Microsoft Word compatible files.

Why did WIRB change the consent form?

WIRB makes changes to consent forms to meet regulatory requirements and to be consistent with information in the protocol. In the "redline" version, the superscript numbers and Legend Reasons for Change provide information about why a change was made.

Why is there a signature block for the person who conducted the consent discussion?

WIRB will automatically include a signature block to be signed by "the person who conducted the informed consent discussion," in compliance with ICH 4.8.8. WIRB does not include a witness signature block unless requested by the site or sponsor.

19. Appendices

A. Appendix 1: Template Consent Form

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	Title
PROTOCOL NO.:	Sponsor WIRB® Protocol #
SPONSOR:	Name
INVESTIGATOR:	Name Address City, State, Zip Code Country
STUDY-RELATED PHONE NUMBER(S):	Name Phone Number(s) (24-hour number required for studies that are more than minimal risk)

[Add the following statement only if the study protocol expressly allows the enrollment of subjects not capable of consenting for themselves:] A person who takes part in a research study is called a research or study subject. In this consent form "you" always refers to the research subject. If you are a legally authorized representative, please remember that "you" means the research (study) subject.

SUMMARY

[The summary section should summarize for the subject what the informed consent process will tell them, including:

- *How research differs from regular health care.*
- *The rights and responsibilities of research subjects.*
- *Information subjects should have before joining a research study.]*

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study: *[remove any that do not apply]*

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational [drug, device, vaccine] is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

PURPOSE OF THE STUDY

[In simple language, explain the following:

- *Why the research is being done*
- *What the experimental components are]*

PROCEDURES

[In simple language and in a simple bullet format, explain the following:

- *The tests and procedures that will be done*
- *Which procedures/drugs are standard care and which are for research purposes only*
- *Whether a placebo or sham procedure will be involved*
- *The chances of being assigned to various study arms*
- *The method of assignment (random, etc.)]*

RISKS AND DISCOMFORTS

[In simple language and in a simple bullet format (whenever possible), explain the possible risks and discomforts:
Start with the side effects for the experimental drugs, devices or procedures. List, for example:

- *most common*

- *less common*
- *rare]*

[Follow with risks and side effects for all drugs, devices or procedures used in the study.]

There may be side effects that are not known at this time.

[If applicable, include any risks relative to pregnancy for both men and women. For example:]
Women who are pregnant or nursing a child may not take part in this study. Before entering the study, you and your study doctor must agree on the method of birth control you will use during the entire study. If you think that you have gotten pregnant during the study, you must tell your study doctor immediately. Pregnant women will be taken out of the study.

Men who are in this research study should not get a sexual partner pregnant while taking the study drug *[If applicable also add the following:]* and for [specify amount of time] after the last dose of study drug. The effect of the study drug on sperm is not known.

[Or other pregnancy language supplied by sponsor—rewrite, if necessary, to simplify]

Other Risks
Your condition may not get better or may get worse during this study.

[If study drug is taken home, insert this or similar language:]
Only you should take the study drug. It must be kept out of the reach of children or anyone else who may not be able to read or understand the label.

NEW INFORMATION
You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
[In simple language indicate the possible benefit for both the subject and future patients.]
Your [name of condition] may improve while you are in this study; however, this cannot be promised. The results of this study may help people with [insert name of condition] in the future.
[or]
It cannot be promised that you will receive any medical benefits from being in this study.

COSTS

[In simple language state:

- *What will be billed to the subject or to their insurance*
- *Who pays if insurance does not (do not use exculpatory language).]*

[For example:]

[Sponsor Name] will provide the study [drug/device] free of charge during this study. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You or your insurance company may be billed for:

- Any standard medical care given during this research study.
- [list other costs as necessary]

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

PAYMENT FOR PARTICIPATION

[Include this section only if subjects will be paid or if the sponsor requires subjects to be told that they will not be paid.]

You will be paid $[Amount] for each completed study visit. If you do not complete the study, you will be paid for the visits you have completed.

[or]

You will not be paid for being in this study.

ALTERNATIVE TREATMENT

If you decide not to enter this study, there are other choices available. These include: *[List the major ones such as drugs / devices / procedures / supportive]*. Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your condition.

[Or]

This is not a treatment study. Your alternative is not to be in this study.

[Use the following authorization format if the site is collecting health information, is a covered entity under HIPAA and is not using a separate HIPAA authorization form.

If the site is not collecting health information, is not a covered entity under HIPAA or is using a separate HIPAA authorization form, use the "Confidentiality" text that follows, rather than the authorization text below.

California sites: This entire HIPAA section plus authorization statement should be placed at the end of the consent form following a page break and must include its own set of signature lines.]

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

Who may use and give out information about you?
The study doctor and the study staff. They may also share the research information with [enter SMO name], an agent for the study doctor *[if no SMO, delete this sentence]*.

Who might get this information?
The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:
- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®).

[Add any institutional names above WIRB.]

Why will this information be used and/or given to others?
- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
Yes, but this permission will not stop automatically.
[or]
This permission will be good until [date] *[required in CA, DE, IN, IL, WA, and WI].*

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Confidentiality *[Use the following confidentiality text if the site is **not** collecting health information, is **not** a covered entity under HIPAA or is using a separate HIPAA authorization form.]*
Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies that are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study [drug or device] may be considered for approval. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor,

delete the following if no CRO or SMO

- [CRO name], an agent for the sponsor,
- [SMO name], an agent for the study doctor,

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA,
- Department of Health and Human Services (DHHS) agencies,
- governmental agencies in other countries, and
- Western Institutional Review Board® (WIRB®).
  [Add any institutional names above WIRB]

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

COMPENSATION FOR INJURY

[Example:]

If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or sponsor.

[or other language supplied by sponsor, simplified.]

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest
- if you do not consent to continue in the study after being told of changes in the research that may affect you
- [if the protocol lists specific reasons, insert the specific reasons for discontinuation listed in protocol]

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

The sponsor [name] will pay for this research study. *[Or other wording, as appropriate].*

QUESTIONS

Contact [name] at [number(s)] for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT
I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the release of my medical and research records for the purpose of this study.
By signing this consent form, I have not given up any of my legal rights.

Signature Block Instructions: Please select the signature section that best reflects the study population.

Example signature block for research involving adults able to consent:

_____
Subject Name (printed)

_____ _____
Signature of Subject Date

Example signature block for research involving adults unable to consent for themselves:

Consent and Assent Instructions:

Consent: Subjects able to provide consent must sign on the subject line below Consent is provided by the Legally Authorized Representative for subjects unable to consent

Assent: Complete the assent signature block below, as applicable.

_____
Subject Name (printed)

CONSENT SIGNATURES:

_____ _____
Signature of Subject (if no Legally Authorized Representative is used) Date

OR

_____ _____
Signature of Legally Authorized Representative Date

_____
Authority of Subject's Legally Authorized Representative or Relationship to Subject

ASSENT SIGNATURES, For Subjects with a Legally Authorized Representative:

Assent:

For subjects who have a legally authorized representative, I confirm that:

- I have explained the study to the extent compatible with the subject's understanding, and the subject has agreed to be in the study.
  OR
- The subject is not able to assent due to lack of mental capacity.

_____ _____
Signature of Person Conducting Assent Discussion Date

Example signature block for research involving children ages 0-17 (please check your state's requirement for age of majority)

Consent and Assent Instructions:

Consent: Subjects 18 years and older must sign on the subject line below
For subjects under 18, consent is provided by the parent or guardian

Assent: Is not required for subjects 6 years and younger
Verbal assent is required for subjects ages 7 through 14 years using the Assent section below [and the Information Sheet for Children].
Verbal assent is required for subjects ages 15 through 17 years using the Assent section below [and the Information Sheet for Adolescents].

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Subject (18 years and older) Date

_____ _____
Signature of Parent or Guardian Date
(when applicable)

ASSENT SECTION:

Statement of person conducting assent discussion:

- I have explained all aspects of the research to the subject to the best of his or her ability to understand.
- I have answered all the questions of the subject relating to this research.
- The subject agrees to be in the research.
- I believe the subject's decision to enroll is voluntary.
- The study doctor and study staff agree to respect the subject's physical or emotional dissent at any time during this research when that dissent pertains to anything being done solely for the purpose of this research.

Statement of Parent or Guardian:

My child appears to understand the research to the best of his or her ability and has agreed to participate.

_____ _____
Signature of Parent or Guardian Date

_____ _____
Printed Name of Person Conducting the Position

Informed Consent Discussion

_____ _____

Signature of Person Conducting the Informed Consent Discussion

Date

Ver. 06/15/2015

B. Appendix 2: Template Information Sheet for Children

RESEARCH SUBJECT INFORMATION SHEET FOR CHILDREN:

TITLE:

PROTOCOL NO.:

SPONSOR:

INVESTIGATOR:

STUDY-RELATED
PHONE NUMBER(S):

You are being asked to participate in a research study because you have _____. Most people with _____ have to take_____. If they do not take _____, _____ may happen.

Our medicine is called _____. We do not know if it is better than other medicines, so we are asking you to help us with this research study. We have used it in other people with _____, but we are still checking to learn more about _____. _____ might not make you feel better, or may make you feel worse.

This study will last _____weeks. You will have to come to the study center __ times. You will be asked questions about _____ and be examined by one of the doctors or nurses.

Blood will be taken from your arm with a needle at ___ different times during the study. You will need to give a urine sample and will have ____(other tests)__.

You will need to take _____ every day.

If the medicine makes you feel different, or if you get ___(side effects)___you must tell your parents or the study doctor.

Important things to know:

- You don't have to do this if you don't want to.
- We won't be mad at you if you decide you don't want to do this.
- Your doctor will still take care of you even if you don't want to do this.

If you are a girl and have started your periods, pregnancy testing will be done. You must use birth control or not have sex during the study. This is because

_____ could cause bad birth defects in babies. You must not take part in this study if you become pregnant. If at any time you think you might be pregnant, you must tell your study doctor right away.

If later you have any questions about this study, please ask your parents or call the study doctor (Dr. _____) or his nurse at _____.

C. Appendix 3: Template Information Sheet for Adolescents

RESEARCH SUBJECT INFORMATION SHEET FOR ADOLESCENTS:

TITLE:

PROTOCOL NO.:

SPONSOR:

INVESTIGATOR:

STUDY-RELATED PHONE NUMBER(S):

You are being asked to participate in a clinical research study. Your decision to be in this study is voluntary. You do not have to participate in this study if you do not want to.

This information sheet will give you information about the risks and benefits of this study so that you can make a better decision about whether you want to take part or not.

PURPOSE OF THE STUDY

The purpose of this research study is _____. You are being asked to be in this study because you have _____.

_____ is approved for treating _____ in adults but is not approved in adolescents or children. In this study, you will receive _____ for at least ___ weeks. After the study, you will be treated with _____.

PROCEDURES

You will be in this study for approximately ___ weeks.

You will have _____visits

Procedures done during this study include a history and examination, blood tests at most visits, and _____.

RISKS AND DISCOMFORTS

Side effects reported with _____ have included _____, _____, _____, _____, _____, _____, _____, _____.

The risks of the blood draw include temporary discomfort from the needle in your arm, bruising, swelling at the needle site and, in rare instances, infection.

Side effects of other study procedures include: _____.

Additional side effects that are unknown at this time could occur during treatment.

The effects of _____ during pregnancy have not been adequately studied. Therefore, there might be unknown risks to the unborn child if you become pregnant during this study. Due to these potential risks you must not participate in this study if you become pregnant, plan to become pregnant during the research study period, or are breast-feeding a child. Pregnancy testing will be done during the study and an acceptable form of birth control (including no sexual intercourse) must be used during the study.

POSSIBLE BENEFITS OF THE STUDY

Your _____ may improve as a result of your participation in this study. However, this cannot be guaranteed. You may not experience any direct health benefits. Information from this study may lead to a better treatment in the future for adolescents and children with _____.

For further information about this study, please refer to the consent form discussed with you for this study.

D. Appendix 4: Pregnant Partner Information Release Form
RESEARCH SUBJECT INFORMATION AND CONSENT FORM

PREGNANT PARTNER INFORMATION RELEASE FORM
For Research Purposes

TITLE:

PROTOCOL NO.:

WIRB® Protocol #

SPONSOR:

INVESTIGATOR:

STUDY-RELATED PHONE NUMBER(S):

Purpose of this Release Form

You became pregnant while your male partner (the biological father of your baby) was taking part in a research study.

With this release form, we are asking for your permission to collect medical information about your pregnancy, its outcome, and if appropriate, the birth and health of your baby. We want to see if the study drug(s) your partner was given have any effect on your pregnancy and/or the health of your baby.

This release form may contain words that you do not understand. Please ask the research study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this release form to think about or discuss with family or friends before making your decision about the collection of your pregnancy information.

If you agree to this collection, we will collect information about your pregnancy, the outcome of your pregnancy, and if appropriate, the birth and the health of your baby. We will give you a signed and dated copy of this release form to keep for your records.

Risks to You

The risk to you from allowing us to collect this information is possible loss of confidentiality of your/your baby's medical records information.

Benefits to You

You will not receive any direct benefit from allowing the collection of information about your pregnancy and its outcome. But what we learn from your information might lead to better understanding of the effect on pregnant women and their unborn babies who are exposed to the study drug taken by the baby's father during a research study.

Costs to You

There will be no cost to you for allowing us to collect this information about your pregnancy.

The regular medical care costs related to your pregnancy and the birth and care of your baby will be billed to you and/or your health insurance in the usual way.

Your Alternative

Your alternative is to not allow us to collect and use this information for research purposes.

Your Decision is Voluntary

Your decision to allow us to collect and use information about your pregnancy and the birth and health of your baby is completely voluntary. If you decide to allow us to collect this information, you can change your mind at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

If you decide not to allow the collection and use of the information, this will not affect medical care for either you or your baby.

Authorization to Use and Disclose Information for Data Collection Purposes

This section of the release form is called an "authorization." It describes the information that we will collect, why we will collect it, and with whom we will share it.

What information about you and your baby might be used and given to others?

The research study doctor will get personal and medical information about your pregnancy and the birth and health of your baby.

Who might use and give out information about you and your baby?

The research study doctor and the study staff.

Who else might get this information?

The sponsor of the research study. "Sponsor" means any people and companies that

- are working for the sponsor,
- are working with the sponsor, or
- are owned by the sponsor.

Your information might also be seen by

- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- [site specific]
- the Western Institutional Review Board® (WIRB®)

Why will your/your baby's information be used and/or given to others?

Your/your baby's information might be used by the research study doctor or others

- to see if the study drug affects you and your baby
- to make sure the research was done right

If the results of the research study are made public, information that could identify you or your baby will not be used.

What if you decide not to give permission (authorization) to use and give out (disclose) your/your baby's information?

Your information and/or your baby's information will not be collected or included in the research study.

Can you review or copy your/your baby's information?

Yes.

Can you withdraw or revoke (cancel) your permission?

Yes, but this permission will not stop automatically.

You can withdraw your permission to use and disclose your/your baby's health information at any time. You do this by writing to the research study doctor.

When you withdraw your permission, no new information that identifies you or your baby will be collected. Information that has already been collected for the research study might still be used and given to others.

Is your/your baby's health information protected after it has been given to others?

There is a risk that your health information and your baby's health information will be given to others without your permission.

If You Have Questions

You can contact the research study doctor, [site specific], at [site specific] for any of the following reasons:

- you have questions about the collection of your/your baby's information or you have questions about the research study that your baby's father is in
- you think you or your baby have a problem related either to the collection of your information or to the research study
- you have questions, concerns, or complaints to report about the collection of your/your baby's information

If you have questions about your/your baby's rights or if you have questions, concerns, or complaints about the research study your male partner is in, you can contact

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, WA 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com.

WIRB is a group of people who perform independent review of research studies.

WIRB will not be able to answer some questions, but you can contact WIRB if the research study staff cannot be reached or if you want to talk to someone other than the research staff.

Do not sign this release form unless you have had a chance to ask questions and you have received satisfactory answers to all your questions.

If you agree to the collection of information about your pregnancy and the birth and health of your baby, you will receive a signed and dated copy of this release form for your records.

Pregnant Partner Signature

I have read the information in this release form (or someone read it to me).

I have had an opportunity to discuss the collection of this information with the research study doctor or research staff. My questions have been answered to my satisfaction.

I agree to allow the collection of information about my pregnancy and the birth and health of my baby.

I authorize the use and disclosure of my information and my baby's information to the parties listed in the authorization section of this release form for the purposes described.

Pregnant Partner's Printed Name _____

_____ _____

Signature of Pregnant Partner Date

(completed by the pregnant partner herself)

12-07-2015 version

E. Appendix 5: Authorization Agreement

Version Date: 03/31/2011

Institutional Review Board (IRB) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A): Western Institutional Review Board

IRB Registration #: IRB00000533 Federalwide Assurance (FWA) #, if any: N/A

Name of Institution Relying on the Designated IRB (Institution B):

_____

FWA #: _____

The Officials signing below agree that ___(*name of Institution B)*___ may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

(___) This agreement applies to all human subjects research covered by Institution B's FWA.

(___) This agreement is limited to the following specific protocol(s):

Name of Research Project:
Name of Principal Investigator:
Sponsor or Funding Agency: _____ Award Number, if any: _____

(___) Other (*describe*):

The review performed by the designated IRB will meet the human subjects protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official: _____ Date: _____
(Institution/Organization A)

Print Full Name: _____ Institutional Title: _____

Signature of Signatory Official: _____ Date: _____
(Institution B)

Print Full Name: _____ Institutional Title: _____

F. Appendix 6: Investigator Guidance

1. PURPOSE

1.1. This guidance describes the obligations of investigators conducting <Human Research> overseen by CGIRB or WIRB.
1.2. For research overseen by an IRB other than CGIRB or WIRB, investigators should follow the requirements of that IRB.

2. GUIDANCE

2.1. Do not commence research until you have the IRB approval letter and obtained all other required approvals, such as radiation safety approval, biosafety approval, and approvals of departments or divisions that require approval of the use of their resources.

2.1.1. If there are any questions about whether you are conducting research involving human subjects, contact the IRB before commencing the study.

2.2. Comply with all requirements and determinations of the IRB.
2.3. Ensure that there are adequate resources to carry out the research safely. This includes, but is not limited to, sufficient investigator time, appropriately qualified research team members, equipment, and space.
2.4. Ensure that research staff are qualified (e.g., including but not limited to appropriate training, education, expertise, credentials, protocol requirements and, when relevant, privileges) to perform procedures and duties assigned to them during the study.
2.5. Personally conduct or supervise the research.
2.6. Conduct the research in accordance with the relevant current protocol approved by the IRB.
2.7. Protect the rights, safety, and welfare of subjects involved in the research.
2.8. Submit proposed modifications to the IRB prior to their implementation.

2.8.1. Do not make modifications to the research without prior IRB review and approval unless necessary to eliminate apparent immediate hazards to subjects.

2.9. Submit continuing reviews when requested by the IRB.
2.10. Submit a closure form to close research (end the IRB's oversight) when:

2.10.1. The protocol is permanently closed to enrollment
2.10.2. All subjects have completed all protocol related interventions and interactions
2.10.3. For research subject to federal oversight other than FDA:

2.10.3.1. No additional identifiable private information about the subjects is being obtained
2.10.3.2. Your analysis of private identifiable information is completed

2.11. If research approval expires, stop all research activities and immediately contact the IRB.
2.12. Promptly report to the IRB the information items listed in "INVESTIGATOR GUIDANCE: Prompt Reporting Requirements (HRP-801)."
2.13. Do not accept or provide payments to professionals in exchange for referrals of potential subjects ("finder's fees.")
2.14. Do not accept payments designed to accelerate recruitment that were tied to the rate or timing of enrollment ("bonus payments") without prior IRB approval.
2.15. For studies regulated by a federal department or agency, follow the additional obligations, as applicable:

2.15.1. "INVESTIGATOR GUIDANCE: Additional DOD Obligations (HRP-810)"
2.15.2. "INVESTIGATOR GUIDANCE: Additional DOE Obligations (HRP-811)"
2.15.3. "INVESTIGATOR GUIDANCE: Additional DOJ Obligations (HRP-812)"
2.15.4. "INVESTIGATOR GUIDANCE: Additional EPA Obligations (HRP-813)"
2.15.5. "INVESTIGATOR GUIDANCE: Additional ED Obligations (HRP-814)"
2.15.6. "INVESTIGATOR GUIDANCE: Additional FDA Obligations (HRP-815)"

2.16. For studies where ICH-GCP compliance is required, follow additional the obligations in "INVESTIGATOR GUIDANCE: Additional ICH-GCP Obligations (HRP-816)."
2.17. When required by the IRB ensure that consent, permission, and assent are obtained and documented in accordance with the relevant current protocol as approved by the IRB.
2.18. Retain research records (including signed consent documents) for the greater of:

2.18.1. Three years after completion of the research
2.18.2. For drug studies conducted under an IND, two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.
2.18.3. For device studies conducted under an IDE or abbreviated IDE, two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
2.18.4. The retention period required by the sponsor
2.18.5. The retention period required by local, state, or international law.

2.18.5.1. HIPAA requires signed authorizations to be retained for six years from the date signed or the date when it last was in effect, whichever is later.

2.18.6. The retention period required by a site that is not part of this [Organization].

3. REFERENCES

3.1. 21 CFR §50, §56

INVESTIGATOR GUIDANCE: Prompt Reporting Requirements

Document No.:	Edition No.:	Effective Date:	Page:
HRP-801	002	28 Sep 2013	Page 1 of 1

1. PURPOSE

1.1. This guidance describes the information to promptly report to CGIRB and WIRB when the research is subject to oversight by CGIRB or WIRB.

1.2. For research overseen by an IRB other than CGIRB or WIRB, investigators should follow the requirements of that IRB.

2. GUIDANCE

2.1. Report the following information items to the IRB within 5 days:

- 2.1.1. New or increased risk[3]
- 2.1.2. Protocol deviation that harmed a subject or placed subject at risk of harm
- 2.1.3. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
- 2.1.4. Audit, inspection, or inquiry by a federal agency
- 2.1.5. Written reports of federal agencies (e.g., FDA Form 483)
- 2.1.6. <Allegation Noncompliance> or <Finding of Noncompliance>
- 2.1.7. Breach of confidentiality
- 2.1.8. Unresolved subject complaint
- 2.1.9. Suspension or premature termination by the sponsor, investigator, or institution
- 2.1.10. Incarceration of a subject in a research study not approved to involve prisoners
- 2.1.11. Adverse events or IND safety reports that require a change to the protocol or consent
- 2.1.12. State medical board actions
- 2.1.13. Unanticipated adverse device effect[4]
- 2.1.14. Information where the sponsor requires prompt reporting to the IRB

2.2. Information not listed above does not require prompt reporting to CGIRB and WIRB.

3. REFERENCES

3.1. 21 CFR §56.108(b)

3.2. 45 CFR §46.103(b)(5)

[3] For example, publications indicating a new risk, new risk in an investigator brochure, FDA black box warning, new risk identified in a data safety monitoring report, information or change that adversely affects subject safety, or information or change that adversely affects the conduct of the research.

[4] Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

1. PURPOSE

1.1. This guidance describes a process that in general is suitable to obtain informed consent.
1.2. Other procedures may be suitable when approved by the IRB.

2. BACKGROUND

2.1. "Person providing consent" means:

- 2.1.1. In the case of a cognitive intact adult, the individual being asked to take part
- 2.1.2. In the case of an adult unable to consent, that individual's LAR
- 2.1.3. In the case of a child:
  - 2.1.3.1. One parent, if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
  - 2.1.3.2. One parent if the IRB determined that permission from one parent was sufficient
  - 2.1.3.3. An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care
  - 2.1.3.4. Both parents

2.2. "Consent information" means:

- 2.2.1. Long form consent document (when the IRB requires the long form of consent documentation)
- 2.2.2. Short form consent document and summary (when the IRB allows the short form of consent documentation)
- 2.2.3. Script or information sheet (when the IRB has approved a waiver of documentation of consent)

2.3. Communicate in the preferred language of the person providing consent
2.4. Unless the IRB affirmatively approved a protocol to include the following populations, such subjects may not be enrolled:

- 2.4.1. Adults unable to consent
- 2.4.2. Children
- 2.4.3. Neonates of uncertain viability
- 2.4.4. Nonviable neonates
- 2.4.5. Pregnant women
- 2.4.6. Prisoners
- 2.4.7. Individuals unable to speak English

2.5. The short form of consent documentation may be use only if affirmatively approved by the IRB.
2.6. For the short form of consent documentation:

- 2.6.1. The short form is a standard template translated into the subject's language.
- 2.6.2. The summary is the English version of the long form.

2.7. For waiver of documentation of consent, the script is the long form without a signature block.

2.8. Interpreters are to be conversant in both English and the language understood by the person providing consent. When allowed by institutional policy, the interpreter may be a member of the research team, or a family member or friend of the subject or person providing consent.

2.9. If the consent process requires an <Impartial Witness>:

2.9.1. The <Impartial Witness> is to be present during the entire consent discussion and to attest that the information in the consent form and any other information provided was accurately explained to, and apparently understood by, the subject/LAR, and that consent was freely given.

2.9.2. The <Impartial Witness> may not be a person involved in the research.

3. GUIDANCE

3.1. Obtain the IRB-approved consent document, short form consent document, or script, as applicable.

3.1.1. Verify that you are using the most current IRB-approved information.

3.1.2. Verify that the consent document, if any, is in language understandable to the person providing consent.

3.2. If the person providing consent cannot read or the short form of consent documentation is used, obtain an <Impartial Witness>.

3.3. If the person providing consent cannot speak English, obtain the services of an interpreter.

3.4. Go over the information in the consent document using language understandable to the person providing consent.

3.4.1. Do not provide any information to the person providing consent through which the person providing consent is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

3.4.2. When providing information about treatments or compensation for injury, provide factual information and avoid statements that imply that compensation or treatment is never available.

3.5. Invite and answer questions.

3.6. Evaluate whether the following is true for the person providing consent. If not, take steps to correct or determine that the person providing consent is incapable of providing consent:

3.6.1. The person providing consent has been provided sufficient information.

3.6.2. The person providing consent understands the information

3.6.2.1. If the person providing consent has a disease or condition that may affect cognition, assess whether the person providing consent has sufficient cognitive capacity to legally provide informed consent.

3.6.2.2. If the subject is pregnant, ensure the person providing consent is fully informed regarding the reasonably foreseeable effect of the research on the fetus or neonate.

3.6.3. The person providing consent does not feel coerced or unduly influenced.

3.6.3.1. Ensure there is no threat of harm or adverse consequences for a decision to not participate.

3.6.3.2. Ensure that outside parties (family or caretakers) do not coerce or unduly influence the person providing consent, especially if that person is vulnerable to coercion or undue influence.

3.6.3.3. Ensure that the amount of payment does not coerce or unduly influence economically disadvantaged individuals.

3.6.3.4. For persons providing consent who are in a subordinate position to a member of the research team (e.g., employee or student), ensure that there is no threat of harm or adverse consequences to the subject's position for a decision to not participate.

3.6.4. The person providing consent has sufficient time to make a decision.

3.6.4.1. Provide the person providing consent with sufficient time to understand the information. Spend as much time as needed

3.6.4.2. Provide the person providing consent with sufficient time to ask questions.

3.6.5. The individual providing consent understands the consequences of a decision.

3.6.6. The individual providing consent can communicate a choice.

3.7. Once a person providing consent indicates that he or she does not want to consent, stop.

3.8. If the subject is a child or adult unable to consent:

3.8.1. Explain the research to the extent compatible with the subject's understanding.

3.8.1.1. Ensure that parents or guardians do not coerce or unduly influence children.

3.8.1.2. Ensure that outside parties (family or caretakers) do not coerce or unduly influence adults unable to consent.

3.8.2. If the IRB determined that assent was a requirement and the subject is capable of being consulted, request the assent (affirmative agreement) of the subject.

3.8.2.1. If the subject indicates that he or she does not want to take part, stop.

4. REFERENCES

4.1. 21 CFR §50.20, §50.25

4.2. 45 CFR §46.116

1. PURPOSE

1.1. This guidance describes a process that in general is suitable to document consent in writing.
1.2. Other procedures may be suitable when approved by the IRB.

2. BACKGROUND

2.1. "Person providing consent" means:

2.1.1. In the case of a cognitive intact adult, the individual being asked to take part
2.1.2. In the case of an adult unable to consent, that individual's LAR
2.1.3. In the case of a child:

2.1.3.1. One parent, if the other parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.
2.1.3.2. One parent if the IRB determined that permission from one parent was sufficient
2.1.3.3. An individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care
2.1.3.4. Both parents

2.2. The short form of consent documentation may be use only if affirmatively approved by the IRB.
2.3. For the short form of consent documentation:

2.3.1. The short form is a standard template translated into the subject's language.
2.3.2. The summary is the English version of the long form.

2.4. If the consent process required an <Impartial Witness>:

2.4.1. The <Impartial Witness> is to be present during the entire consent discussion and to attest that the information in the consent form and any other information provided was accurately explained to, and apparently understood by, the subject/LAR, and that consent was freely given.
2.4.2. The <Impartial Witness> may not be a person involved in the research.

3. GUIDANCE

3.1. If the consent process will be documented with the long form:

3.1.1. Verify that the document is in language understandable to the person providing consent.
3.1.2. If the IRB required written documentation of assent, note one of the following:

3.1.2.1. Assent was obtained.
3.1.2.2. Assent was not obtained because the capability of the subject is so limited that the subject cannot reasonably be consulted.

3.1.3. Have the following individuals personally sign and date the consent document:

3.1.3.1. Person giving consent
3.1.3.2. Person obtaining consent
3.1.3.3. <Impartial Witness>, if any

3.2. If the consent process will be documented with the short form:

3.2.1. Verify that the document is in language understandable to the person providing consent.
3.2.2. If the IRB required written documentation of assent, note one of the following:

3.2.2.1. Assent of the child was obtained.
3.2.2.2. Assent of the child was not obtained because the capability of the child is so limited that the child cannot reasonably be consulted.

3.2.3. Have the following individuals personally sign and date the consent document:

3.2.3.1. Person giving consent
3.2.3.2. Person obtaining consent
3.2.3.3. <Impartial Witness>

3.2.4. Have the following individuals personally sign and date the summary:

3.2.4.1. Person giving consent
3.2.4.2. Person obtaining consent
3.2.4.3. <Impartial Witness>

3.3. Provide the person providing consent with copies of the signed and dated documents.

3.3.1. This may be accomplished either by making a photocopy or by having individuals sign and date two copies.

3.4. File a copy of the consent document with the medical record when required by local policy.
3.5. Retain the signed and dated documents in the study records for the greater of:

3.5.1. Three years after completion of the research
3.5.2. For drug studies conducted under an IND, two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.
3.5.3. For device studies conducted under an IDE or abbreviated IDE, two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.
3.5.4. The retention period requested by the sponsor.
3.5.5. The retention period required by local, state, or international law.
3.5.6. The retention period required by a site that is not part of this [Organization].

4. REFERENCES

4.1. 21 CFR §50.27, 56.115(b), §312.62(c), §812.140(d)

4.2. 45 CFR §46.115(b), §46.117

1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting DOD research.

2. GUIDANCE

2.1. Training and education

2.1.1. All personnel who conduct, review, approve, oversee, support, or manage human subjects research are required to undergo initial and continuing research ethics education.
2.1.2. There may be specific DOD educational requirements or certification required.
2.1.3. DOD may evaluate the organization's education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.
2.1.4. As the investigator, you must be aware of the specific requirements contained in DOD regulations and requirements and educated about these requirements when appropriate.

2.2. Scientific Review

2.2.1. The IRB must consider the scientific merit of the research.
2.2.2. The IRB may rely on outside experts to provide an evaluation of the scientific merit.

2.3. International Research

2.3.1. You or the organization must obtain permission to conduct research in that country by certification or local ethics review.
2.3.2. You must follow all local laws, regulations, customs, and practices.

2.4. Reporting: The following findings in DOD-supported research must be reported to the DOD human research protection officer within 30 days:

2.4.1. Determinations of <Serious Noncompliance> or <Continuing Noncompliance>
2.4.2. Significant changes to the research protocol that are approved by the IRB
2.4.3. The results of the IRB continuing review
2.4.4. Change of reviewing IRB
2.4.5. When the organization is notified by any Federal department, agency or national organization that any part of an HRPP is under investigation for cause requirements
2.4.6. <Unanticipated Problems Involving Risk to Subjects or Others>
2.4.7. <Suspension of IRB approval>
2.4.8. <Termination of IRB approval>

2.5. Survey Approval

2.5.1. Surveys performed on DOD personnel must be submitted, reviewed, and approved by the DOD after the research protocol is approved by the IRB.

2.6. Multisite Research

2.6.1. When conducting multi-site research, a formal agreement between organizations is required to specify the roles and responsibilities of each party.

2.7. Definition of <Minimal Risk>

2.7.1. The definition of the minimal risk based on the phrase “ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests” must not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

2.7.2. The organization applies this definition to all research regardless of funding.

2.8. Appointment of a Research Monitor:

2.8.1. This is required for research involving greater than minimal risk.

2.8.2. The IRB or institutional official can require a research monitor for a portion of the research or studies involving no more than minimal risk, if appropriate.

2.8.3. The research monitor is appointed by name and must be independent of the team conducting the research.

2.8.4. There may be more than one research monitor (e.g. if different skills or experience are needed).

2.8.5. The monitor may be an ombudsman or a member of the data safety monitoring board. The IRB must approve a written summary of the monitors’ duties, authorities, and responsibilities.

2.8.6. The IRB or institutional official must communicate with research monitors to confirm their duties, authorities, and responsibilities.

2.8.7. The duties of the research monitor are determined on the basis of specific risks or concerns about the research.

2.8.7.1. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and <Unanticipated Problems Involving Risk to Subjects or Others>, oversee data matching, data collection and analysis).

2.8.7.2. The research monitor may discuss the research protocol with investigators, interview human subjects, and consult with others outside of the study.

2.8.7.3. Report observations and findings to the IRB or a designated official.

2.8.8. The research monitor has the authority to:

2.8.8.1. Stop a research study in progress.

2.8.8.2. Remove individuals from study.

2.8.8.3. Take any steps to protect the safety and well-being of subjects until the IRB can assess.

2.8.9. Recruitment of Service Members

2.8.9.1. Officers are not permitted to influence the decision of their subordinates.

2.8.9.2. Officers and senior non-commissioned officers may not be present at the time of recruitment.
2.8.9.3. Officers and senior non-commissioned officers have a separate opportunity to participate.
2.8.9.4. When recruitment involves a percentage of a unit, an independent ombudsman is present.

2.8.10. Compensation of Service Members:

2.8.10.1. Service member may not receive pay or compensation for research during duty hours.
2.8.10.2. A service member may be compensated for research if the subject is involved in the research when not on duty.
2.8.10.3. Federal employees while on duty and non-Federal persons may be compensated for blood draws for research up to $50 for each blood draw.
2.8.10.4. Non-Federal persons may be compensated for participating in research involving other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research.

2.9. Consent

2.9.1. The disclosure for research-related injury must follow the requirements of the DOD component.
2.9.2. If the subject undergoes interactions or interventions for research purposes, the subject is considered an "experimental subject." For experimental subjects:

2.9.2.1. A waiver of the consent process is prohibited unless a waiver is obtained from the Assistant Secretary of DOD for Research and Engineering.
2.9.2.2. The Assistant Secretary for DOD for Research and Engineering may waive the requirements for consent when all of the following are met:

2.9.2.2.1. The research is necessary to advance the development of a medical product for the Military Services.
2.9.2.2.2. The research may directly benefit the individual experimental subject.
2.9.2.2.3. The research is conducted in compliance with all other applicable laws and regulations.

2.9.2.3. The IRB may waive the consent process for subjects who are not "experimental subjects."
2.9.2.4. If consent is to be obtained from the experimental subjects' legal representative, the research must intend to benefit the individual subject.

2.9.2.4.1. The determination that research is intended to be beneficial to the individual experimental subject must be made by an IRB.

2.9.3. Waivers of consent are prohibited for classified research.

2.10. Research on Pregnant Women

2.10.1. Research involving pregnant women and fetuses as subjects is subject to HHS Subpart B except:

2.10.1.1. The phrase “biomedical knowledge” is replaced with “generalizable knowledge.”

2.10.1.2. The applicability of Subpart B is limited to research involving pregnant women as subjects in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as subjects.

2.11. Research on Prisoners

2.11.1. Research involving prisoners is subject to HHS Subparts C.

2.11.2. Research involving prisoners cannot be reviewed by the expedited procedure.

2.11.3. When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.

2.11.4. In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:

2.11.4.1. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.

2.11.4.2. The research presents no more than minimal risk.

2.11.4.3. The research presents no more than an inconvenience to the subject.

2.11.5. When a subject becomes a prisoner, if the investigator asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-subject may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the institutional official and DOD Component office review the IRB’s approval to change the research protocol. Otherwise, the IRB chair must require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, must promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject’s confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

2.11.6. Research involving a detainee as a human subjects is prohibited.

2.11.6.1. This prohibition does not apply to research involving investigational drugs and devices when the same products would be offered to US military personnel in the same location for the same condition.

2.11.7. Research involving prisoners of war is prohibited.

2.11.7.1. "Prisoner of war" includes any person captured, detained, held, or otherwise under the control of DOD personnel (military, civilian, or contractor employee). Such persons include: Enemy Combatant, Lawful Enemy Combatant, Unlawful Enemy Combatant, Enemy Prisoner of War, Retained Person, and Civilian Internee. Such persons do not include personnel of the DOD being held for law enforcement purposes. It does not include persons being held primarily for law enforcement purposes, except where the United States is the occupying power.

2.11.7.2. This prohibition does not apply to activities covered by investigational new drug or investigational device provisions for the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to FDA regulations for investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices.

2.12. Research on Children

2.12.1. Research involving children is subject to the HHS Subpart D.

2.12.2. The exemption for research involving survey or interview procedures or observation of public behavior, does not apply to research with children, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.

2.13. Research on Fetal Tissue

2.13.1. Fetal research must comply with US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.

2.14. Waiver of Informed consent for Planned Emergency Research

2.14.1. An exception from consent in emergency medicine research is prohibited unless a waiver is obtained from the Secretary of DOD.

2.15. Records

2.15.1. Records maintained that document compliance or <Noncompliance> with DOD regulations must be made accessible for inspection and copying by representatives of the DOD at reasonable times and in a reasonable manner as determined by the supporting DOD component.

2.16. Non-exempt Classified Research

2.16.1. The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process and Information provided by the subjects during the course of the research.

2.16.2. Secretary of DOD approval is required for all classified non-exempt research involving subjects.

2.16.2.1. Submission for approval must be from the Head of the OSD or DOD Component conducting or supporting the non-exempt research involving human subjects. The request must be coordinated with the ASD(R&E) and General Counsel of the Department of DOD after the IRB has approved the research.

2.16.3. Waivers of informed consent are prohibited.

2.16.4. Informed consent procedures must include:

2.16.4.1. Identification of the DOD as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of DOD may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.

2.16.4.2. A statement that the research involving human subjects is classified and an explanation of the impact of the classification.

2.16.5. IRB approval process must meet the following requirements:

2.16.5.1. IRB review must be conducted using a full board review. Use of an expedited review procedure is prohibited.

2.16.5.2. At least one non-affiliated member must be a non-Federal employee (other than as an individual appointed as an expert or consultant for purposes of service on the IRB).

2.16.5.3. Any IRB member who disagrees with a majority decision approving a project may appeal the decision to the Secretary of DOD. The appeal must be included in the DOD Component's submission to the Secretary of DOD.

2.16.5.4. The IRB must determine whether potential subjects need access to classified information to make a valid, informed consent decision.

2.16.6. Disclosure or use of classified information must comply with DOD requirements for access to and protection of classified information.

3. REFERENCES

3.1. 10 USC 980
3.2. DOD Instruction 3216.02
3.3. DOD Instruction 3216.2
3.4. OPNAVINST 5300.8B
3.5. SECNAVINST 3900.39D

4. PURPOSE

4.1. This guidance outlines the additional obligations of investigators conducting DOE research.

5. GUIDANCE

5.1. DOE-funded or DOE laboratory-managed or conducted projects involving intentional modification of an individual's or a group of individuals' environment must be managed as human subjects research and subject to the requirements of DOE Order 443.1B.

5.1.1. Where "generalizable" should be viewed in terms of contribution to knowledge within the specific field of study, this includes:

5.1.1.1. Studies in human environments (e.g., occupied homes and offices, classrooms, and transit centers like subway systems and airports) that use tracer chemicals, particles, and/or other materials, such as perfluorocarbons, to characterize airflow.

5.1.1.2. Studies in occupied homes and/or offices that:

5.1.1.2.1. Manipulate the environment to achieve research aims, e.g., increasing humidity and/or reducing influx of outside air through new energy-saving ventilation systems.

5.1.1.2.2. Test new materials (e.g., sequentially changing the filter materials in the HVAC system while monitoring the effects on air quality and energy use).

5.1.1.2.3. Involve collecting information on occupants' views of appliances, materials, or devices installed in their homes or their energy saving behaviors through surveys and focus groups. Some surveys may be online surveys administered through providers such as Amazon Mechanical Turk and Survey Monkey.

5.1.2. Even if the IRB does not view a project as meeting the literal definition of human subjects research as defined in 45 CFR Part 46, DOE requires initial review by the IRB of the application and supporting materials to determine whether the individuals included in the research will be properly informed and protected. Adherence to each specific requirement of 45 CFR Part 46 is not required in such a case, but DOE does require that:

5.1.2.1. An application and supporting materials be submitted to the IRB;

5.1.2.2. The Chair decide the level of review;

5.1.2.3. During the review, the IRB assess risks associated with the research and whether the individuals to be included in such research will be properly informed and protected. SMEs should be used, as needed, in assessing risks and in determining whether risks have been mitigated to the extent practicable (to minimal risk).

5.1.2.4. After the review, the Chair send a letter to the PI indicating that the project has been reviewed in accordance with DOE

expectations and will be monitored and tracked by the IRB, which means that the PI will:

5.1.2.4.1. Implement any IRB recommendations before the project begins;
5.1.2.4.2. Notify the IRB of any proposed changes to the protocol in the future and ensure IRB review and authorization to proceed before implementing these changes;
5.1.2.4.3. Provide an annual update to the IRB; and
5.1.2.4.4. Follow the notification and reporting requirements in DOE O 443.1B for reporting adverse events, annual update of the DOE HSRD, etc.

5.2. Within 48 hours of the following (or within 24 hours if private identifiable information is involved), provide a description of corrective actions taken immediately following the incident, as well as corrective actions to be taken for concurrence by the appropriate DOE HRPP Manager:

5.2.1. Any significant adverse events, unanticipated problems, and complaints about the research,
5.2.2. Any <Suspension of IRB Approval> <Termination of IRB Approval>;
5.2.3. Any significant <Noncompliance> with HRPP procedures or other requirements, which shall be reported to the IRB for evaluation for further action with the appropriate DOE Human Subject Protection Program Manager

5.3. In accordance with the DOE "Checklist for IRBs to Use in Verifying that HS Research Protocols are In Compliance with DOE Requirements," your research protocol must include description of processes for:

5.3.1. Keeping private identifiable information confidential
5.3.2. Releasing private identifiable information only under a procedure approved by the responsible IRB(s) and DOE, where required
5.3.3. Using private identifiable information only for purposes of the DOE-approved research
5.3.4. Handling and marking documents containing private identifiable information as "containing private identifiable information" or "containing protected health information"
5.3.5. Establishing reasonable administrative, technical, and physical safeguards to prevent unauthorized use or disclosure of private identifiable information
5.3.6. Making no further use or disclosure of the private identifiable information except when approved by the responsible IRB and DOE, where applicable, and then only:

5.3.6.1. In an emergency affecting the health or safety of any individual
5.3.6.2. For use in another research project under these same conditions and with DOE written authorization
5.3.6.3. For disclosure to a person authorized by the DOE program office for the purpose of an audit related to the project or when required by law.

5.3.7. Protecting private identifiable information data stored on removable media using encryption products that are Federal Information Processing Standards (FIPS) 140-2 certified

5.3.8. Using FIPS 140-2 certified encryption that meet the current DOE password requirements cited in DOE Guide 205.3-1

5.3.9. Shipping removable media containing PII, as required, by express overnight service with signature and tracking capability, and shipping hard copy documents double wrapped via express overnight service

5.3.10. Encrypting data files containing PII that are being sent by e-mail with FIPS 140-2 certified encryption products

5.3.11. Sending passwords that are used to encrypt data files containing PII separately from the encrypted data file, i.e. separate e-mail, telephone call, separate letter

5.3.12. Using FIPS 140-2 certified encryption methods for websites established for the submission of information that includes PII

5.3.13. Using two-factor authentication for logon access control for remote access to systems and databases that contain PII. (Two-factor authentication is contained in the National Institute of Standards and Technology (NIST) Special Publication 800-63 Version 1.0.2 found at: http://csrc.nist.gov/publications/nistpubs/800-63/SP800-63V1_0_2.pdf)

5.3.14. In addition to other reporting requirements, reporting the loss or suspected loss of PII immediately (within 5 business days) upon discovery to: 1) the DOE Project Officer and 2) the applicable IRBs.

6. REFERENCES

6.1. 10 CFR 745

6.2. DOE Order 443.1.B

6.3. Checklist for IRBs to Use in Verifying That HS Research Protocols Are in Compliance with DOE Requirements

INVESTIGATOR GUIDANCE: Additional DOJ Obligations

Document No.:	Edition No.:	Effective Date:	Page:
HRP-812	001	06 Sep 2013	Page 1 of 4

1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting DOJ research.

2. GUIDANCE

2.1. National Institute of Justice (NIJ)-funded research

2.1.1. Investigators must have a privacy certificate approved by the NIJ human subjects protection officer.

2.1.2. Investigators and research staff must sign employee confidentiality statements, and investigators must maintain these statements.

2.1.3. Investigators must obtain written informed consent and disclose

2.1.3.1. The names of the funding agencies.

2.1.3.2. A statement describing the extent to which confidentiality of records identifying the subject will be maintained.

2.1.3.3. Private, identifiable information will be kept confidential and will only be used for research and statistical purposes or if, due to sample size or some unique feature, the identity of the individual cannot be maintained, a statement to that effect.

2.1.3.3.1. What information will be disclosed, under what circumstances, and to whom.

2.1.3.3.2. Any risks that might result from this disclosure

2.1.3.4. The research team does not have to report child abuse unless the subject signs another consent document to allow child abuse reporting.

2.1.4. Investigators must send to the National Archive of Criminal Justice Data a de-identified copy of all data with copies of the informed consent document, data collection instruments, surveys, or other relevant research materials.

2.2. Research conducted within the Bureau of Prisons

2.2.1. The Department of Justice does not consider implementation of Bureau of Prisons programmatic or operational initiatives made through pilot projects to be research.

2.2.2. Investigators must follow the requirements of 28 CFR 512, including:

2.2.2.1. The research must not involve medical experimentation, cosmetic research, or pharmaceutical testing.

2.2.2.2. The research design must be compatible with both the operation of prison facilities and protection of human subjects.

2.2.2.3. The investigator must observe the rules of the institution or office in which the research is conducted.

2.2.2.4. Any investigator who is not an employee of the Bureau of Prisons must sign a statement in which the investigator agrees to adhere to the requirements of 28 CFR 512.

2.2.2.5. The Bureau of Prisons IRB must approve the research.

2.2.2.6. The research must have an adequate research design and contribute to the advancement of knowledge about corrections.

2.2.2.7. The selection of subjects within any one organization must be equitable.

2.2.2.8. Incentives may not be offered to help persuade inmate subjects to participate. Soft drinks and snacks to be consumed at the test setting may be offered.

2.2.2.9. Reasonable accommodations such as nominal monetary recompense for time and effort may be offered to non-confined research subjects who are both:

2.2.2.9.1. No longer in Bureau of Prisons custody

2.2.2.9.2. Participating in authorized research being conducted by Bureau of Prisons employees or contractors

2.2.2.10. A non-employee of the Bureau of Prisons may receive records in a form not individually identifiable when advance adequate written assurance that the record will be used solely as a statistical research or reporting record is provided to the agency.

2.2.2.11. Except as noted in the consent statement to the subject, the investigator must not provide research information that identifies a subject to any person without that subject's prior written consent to release the information. For example, research information identifiable to a particular individual cannot be admitted as evidence or used for any purpose in any action, suit, or other judicial, administrative, or legislative proceeding without the written consent of the individual to whom the data pertain.

2.2.2.12. Except for computerized data records maintained at an official Department of Justice site, records that contain non-disclosable information directly traceable to a specific person may not be stored in, or introduced into, an electronic retrieval system.

2.2.2.13. If the investigator is conducting a study of special interest to the Office of Research and Evaluation (ORE) but the study is not a joint research involving ORE, the investigator may be asked to provide ORE with the computerized research data, not identifiable to individual subjects, accompanied by detailed documentation. These arrangements must be negotiated prior to the beginning of the data collection phase of the research.

2.2.2.14. Consent documents must disclose:

2.2.2.14.1. Identification of the investigators.

2.2.2.14.2. Anticipated uses of the results of the research.

2.2.2.14.3. A statement that participation is completely voluntary and that the subject may withdraw consent and end participation in the research at any time without penalty or prejudice (the inmate will be returned to regular assignment or activity by staff as soon as practicable).

2.2.2.14.4. A statement regarding the confidentiality of the research information and exceptions to any guarantees of confidentiality required by

federal or state law. For example, an investigator may not guarantee confidentiality when the subject indicates intent to commit future criminal conduct or harm himself or herself or someone else, or, if the subject is an inmate, indicates intent to leave the facility without authorization.

2.2.2.14.5. A statement that participation in the research will have no effect on the inmate subject's release date or parole eligibility.

2.2.3. Investigators must have academic preparation or experience in the area of study of the proposed research.

2.2.4. When submitting a research protocol, investigators must provide the following information:

2.2.4.1. A summary statement, which includes:

2.2.4.1.1. Names and current affiliations of the investigators.
2.2.4.1.2. Title of the study.
2.2.4.1.3. Purpose of the study.
2.2.4.1.4. Location of the study.
2.2.4.1.5. Methods to be employed.
2.2.4.1.6. Anticipated results.
2.2.4.1.7. Duration of the study.
2.2.4.1.8. Number of subjects (staff or inmates) required and amount of time required from each.
2.2.4.1.9. Indication of risk or discomfort involved as a result of participation.

2.2.4.2. A comprehensive statement, which includes:

2.2.4.2.1. Review of related literature.
2.2.4.2.2. Detailed description of the research method.
2.2.4.2.3. Significance of anticipated results and their contribution to the advancement of knowledge.
2.2.4.2.4. Specific resources required from the Bureau of Prisons.
2.2.4.2.5. Description of all possible risks, discomforts, and benefits to individual subjects or a class of subjects, and a discussion of the likelihood that the risks and discomforts will actually occur.

2.2.4.2.5.1. Description of steps taken to minimize any risks.

2.2.4.2.6. Description of physical or administrative procedures to be followed to:

2.2.4.2.6.1. Ensure the security of any individually identifiable data that are being collected for the study.

2.2.4.2.6.2. Destroy research records or remove individual identifiers from those records when the research has been completed.

2.2.4.2.7. Description of any anticipated effects of the research study on organizational programs and operations.

2.2.4.2.8. Relevant research materials such as vitae, endorsements, sample consent statements, questionnaires, and interview schedules.

2.2.4.2.9. A statement regarding assurances and certification required by federal regulations, if applicable.

2.2.5. Investigators must assume responsibility for actions of any person engaged to participate in the research as an associate, assistant, or subcontractor to the investigator.

2.2.6. At least once a year, investigators must provide the Chief, Office of Research and Evaluation, with a report on the progress of the research.

2.2.7. At least 12 working days before any report of findings is to be released, investigators must distribute one copy of the report with an abstract in the report of findings to each of the following:

2.2.7.1. The chairperson of the Bureau Research Review Board
2.2.7.2. The regional director
2.2.7.3. The warden of each institution that provided data or assistance

2.2.8. In any publication of results, investigators must acknowledge the Bureau's participation in the research.

2.2.9. Investigators expressly disclaim approval or endorsement of the published material as an expression of the policies or views of the Bureau.

2.2.10. Prior to submitting for publication the results of research conducted under this subpart, investigators must provide two copies of the material, for informational purposes only, to the Chief, Office of Research and Evaluation, Central Office, Bureau of Prisons.

3. REFERENCES

3.1. 28 CFR §22,
3.2. 28 CFR §512

1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting ED research.

2. GUIDANCE

2.1. For research funded by the National Institute on Disability and Rehabilitation Research, when the IRB reviews research that purposefully requires inclusion of children with disabilities or individuals with mental disabilities as research subjects, the IRB includes at least one person primarily concerned with the welfare of these research subjects.

2.2. The Family Educational Rights and Privacy Act (FERPA) applies when investigators obtain student records or personal education information from an education program as defined as any program principally engaged in the provision of education, including, but not limited to, early childhood education, elementary and secondary education, postsecondary education, special education, job training, career and technical education, and adult education. FERPA requirements include:

2.2.1. An educational agency or institution may disclose personally identifiable information from an education record of a student without consent if the disclosure is part of an agreement between organizations or subjects conducting studies for, or on behalf of, educational agencies or institutions to:

2.2.1.1. Develop, validate, or administer predictive tests
2.2.1.2. Administer student aid programs
2.2.1.3. Improve instruction

2.2.2. A school district or postsecondary institution that uses this exception is required to enter into a written agreement with the organization conducting the research that specifies:

2.2.2.1. The determination of the exception
2.2.2.2. The purpose, scope, and duration of the study
2.2.2.3. The information to be disclosed
2.2.2.4. That information from education records may only be used to meet the purposes of the study stated in the written agreement and must contain the current requirements in Department of Education regulations on redisclosure and destruction of information
2.2.2.5. That the study will be conducted in a manner that does not permit personal identification of parents and students by anyone other than representatives of the Organization with legitimate interests
2.2.2.6. That the Organization is required to destroy or return all personally identifiable information when no longer needed for the purposes of the study
2.2.2.7. The time period during which the Organization must either destroy or return the information

2.2.3. Education records may be released without consent under FERPA if all personally identifiable information has been removed including:

2.2.3.1. Student's name and other direct personal identifiers, such as the student's social security number or student number

2.2.3.2. Indirect identifiers, such as the name of the student's parent or other family members; the student's or family's address, and personal characteristics or other information that would make the student's identity easily traceable; and date and place of birth and mother's maiden name

2.2.3.3. Biometric records, including one or more measurable biological or behavioral characteristics that can be used for automated recognition of an individual, including fingerprints, retina and iris patterns, voiceprints, DNA sequence, facial characteristics, and handwriting.

2.2.3.4. Other information that, alone or in combination, is linked or linkable to a specific student that would allow a reasonable person in the school community, who does not have personal knowledge of the relevant circumstances, to identify the student with reasonable certainty.

2.3. For certain types of research directly funded by ED the Protection of Pupil Rights Amendment (PPRA) applies.

2.3.1. PPRA prohibits students from being required, as part of any research project, to submit without prior consent to surveys, psychiatric examination, testing, or treatment, or psychological examination, testing, or treatment, in which the primary purpose is to reveal information concerning one or more of the following:

2.3.1.1. Political affiliations or beliefs of the student or the student's parent

2.3.1.2. Mental or psychological problems of the student or the student's family

2.3.1.3. Sex behavior or attitudes

2.3.1.4. Illegal, anti-social, self-incriminating, or demeaning behavior

2.3.1.5. Critical appraisals of other individuals with whom respondents have close family relationships

2.3.1.6. Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers

2.3.1.7. Religious practices, affiliations, or beliefs of the student or student's parent

2.3.1.8. Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program

2.3.2. For certain types of research projects not directly funded by ED and conducted in a school that receives funding from ED: Policies and procedures include a process to verify compliance with ED regulations that schools are required to develop and adopt policies in conjunction with parents regarding the following:

2.3.2.1. The right of a parent of a student to inspect, upon the request of the parent, a survey created by a third party before the survey is administered or distributed by a school to a student

2.3.2.1.1. Any applicable procedures for granting a request by a parent for reasonable access to such

survey within a reasonable period of time after the request is received

2.3.2.2. Arrangements to protect student privacy that are provided by the agency in the event of the administration or distribution of a survey to a student containing one or more of the following items (including the right of a parent of a student to inspect, upon the request of the parent, any survey containing one or more of such items):

2.3.2.2.1. Political affiliations or beliefs of the student or the student's parent
2.3.2.2.2. Mental or psychological problems of the student or the student's family
2.3.2.2.3. Sex behavior or attitudes
2.3.2.2.4. Illegal, anti-social, self-incriminating, or demeaning behavior
2.3.2.2.5. Critical appraisals of other individuals with whom respondents have close family relationships
2.3.2.2.6. Legally recognized privileged or analogous relationships, such as those of lawyers, physicians, and ministers
2.3.2.2.7. Religious practices, affiliations, or beliefs of the student or the student's parent
2.3.2.2.8. Income (other than that required by law to determine eligibility for participation in a program or for receiving financial assistance under such program)

2.3.2.3. The right of a parent of a student to inspect, upon the request of the parent, any instructional material used as part of the educational curriculum for the student

2.3.2.3.1. Any applicable procedures for granting a request by a parent for reasonable access to instructional material received

2.3.2.4. The administration of physical examinations or screenings that the school or agency may administer to a student

2.3.2.5. The collection, disclosure, or use of personal information collected from students for the purpose of marketing or for selling that information (or otherwise providing that information to others for that purpose), including arrangements to protect student privacy that are provided by the agency in the event of such collection, disclosure, or use.

2.3.2.5.1. The right of a parent of a student to inspect, upon the request of the parent, any instrument used in the collection of personal information before the instrument is administered or distributed to a student
2.3.2.5.2. Any applicable procedures for granting a request by a parent for reasonable access to such instrument within a reasonable period of time after the request is received

2.4. Access to instructional material used in a research or experimentation program:

2.4.1. All instructional material, including teachers' manuals, films, tapes, or other supplementary instructional material, which will be used in connection with any research or experimentation program or project must be available for inspection by the parents or guardians of the children engaged in such research.

2.5. Definitions:

2.5.1. “Prior consent” means:

2.5.1.1. Prior consent of the student, if the student is an adult or emancipated minor

2.5.1.2. Prior written consent of the parent or guardian, if the student is not an emancipated minor

2.5.2. “Research or experimentation program or project” means any program or project in any research that is designed to explore or develop new or unproven teaching methods or techniques.

2.5.3. “Children” are persons enrolled in research not above the elementary or secondary education level, who have not reached the age of majority as determined under state law.

2.5.4. "Psychiatric or psychological examination or test" means a method of obtaining information, including a group activity, that is not directly related to academic instruction and that is designed to elicit information about attitudes, habits, traits, opinions, beliefs or feelings (34 CFR §98.4)

2.5.5. "Psychiatric or psychological treatment" means an activity involving the planned, systematic use of methods or techniques that are not directly related to academic instruction and that is designed to affect behavioral, emotional, or attitudinal characteristics of an individual or group (34 CFR §98.4)

3. REFERENCES

3.1. 34 CFR §98
3.2. 34 CFR §99
3.3. 34 CFR §356

1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting EPA research.

2. GUIDANCE

2.1. EPA regulates research that is conducted or supported by EPA.
2.2. EPA regulates research whose results are intended to be submitted to EPA, regardless of whether the research is conducted or supported by EPA or any federal agency.
2.3. “Research involving intentional exposure of a human subject” means a study of a substance in which the exposure to the substance experienced by a human subject participating in the study would not have occurred but for the human subject's participation in the study.
2.4. “Observational research” means any human research that is not research involving intentional exposure of a human subject.
2.5. Research involving the intentional exposure of pregnant women, nursing women, or children to any substance is prohibited.
2.6. Observational research involving children must meet the criteria in category (1) or (2) of “CHECKLIST: Research Involving Children (HRP-310)”
2.7. Observational research involving pregnant women must meet the criteria in “CHECKLIST: Pregnant Women (HRP-305).”
2.8. Research approved by the IRB must be submitted to the EPA human subjects research review official for final review and approval before the research can begin.

3. REFERENCES

3.1. 40 CFR §26
3.2. EPA Order 1000.17 Change A1

1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting FDA research.

2. GUIDANCE

2.1. For all FDA-regulated research:

2.1.1. When a subject withdraws from a study:

2.1.1.1. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

2.1.1.1.1. The consent document cannot give the subject the option of having data removed.

2.1.1.2. You may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

2.1.1.3. If a subject withdraws from the interventional portion of the study, but agrees to continued follow-up of associated clinical outcome information as described in the previous bullet, you must obtain the subject's informed consent for this limited participation in the study (assuming such a situation was not described in the original informed consent form). IRB approval of informed consent documents is required.

2.1.1.4. If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, you must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent.

2.1.1.4.1. You may review study data related to the participant collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

2.1.2. The Responsible Party for a clinical trial must register the trial and submit results information.

2.1.2.1. A principal investigator of a clinical trial is the Responsible Party if the clinical trial is investigator initiated or if so designated by a sponsor, grantee, contractor, or awardee.

2.1.2.2. Registration is required for the following trials:

2.1.2.2.1. Controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products
2.1.2.2.2. Controlled trials with health outcomes of devices, other than small feasibility studies
2.1.2.2.3. Pediatric post-market surveillance required by FDA

2.2. Requirements for studies conducted under an IND

2.2.1. You, or any person acting on your behalf, cannot represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.

2.2.1.1. This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

2.2.2. You may not commercially distribute or test market an investigational new drug.

2.2.3. Ensure that the 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 your care; and for the control of drugs under investigation.

2.2.4. Obtain the informed consent of each human subject to whom the drug is administered, unless:

2.2.4.1. Waived by the IRB for planned emergency research.
2.2.4.2. Where the requirements in “WORKSHEET: Emergency Use - Drugs and Biologics (HRP-451)” are met

2.2.5. Maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects.

2.2.5.1. If the investigation is terminated, suspended, discontinued, or completed, return the unused supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies as directed by the sponsor.

2.2.6. Prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

2.2.6.1. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual’s hospital chart(s), and the nurses’ notes.
2.2.6.2. The case history for each individual must document that informed consent was obtained prior to participation in the study.

2.2.7. Retain research records for the greater of:

2.2.7.1. Three years after completion of the research

2.2.7.2. For drug studies conducted under an IND, two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

2.2.7.3. For device studies conducted under an IDE or abbreviated IDE, two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

2.2.7.4. The retention period requested by the sponsor.

2.2.8. Furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained.

2.2.9. Immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure.

2.2.9.1. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

2.2.9.2. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, immediately report the event to the sponsor.

2.2.9.3. Record non-serious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

2.2.10. Provide the sponsor with an adequate report shortly after completion of your participation in the investigation.

2.2.11. Provide the sponsor with sufficient accurate financial information to allow an applicant to submit complete and accurate certification or disclosure statements as required under part 54 of this chapter.

2.2.11.1. Promptly update this information if any relevant changes occur during the course of the investigation and for one year following the completion of the study.

2.2.12. Assure that an IRB that complies with the requirements set forth in FDA regulations will be responsible for the initial and continuing review and approval of the proposed clinical study.

2.2.12.1. Promptly report to the IRB all changes in the research activity and all <Unanticipated Problems Involving Risk to Subjects or Others>.

2.2.12.2. Make no changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

2.2.13. 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 of your records or reports.

2.2.13.1. You are not required to divulge subject 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.

2.2.14. If the investigational drug is subject to the Controlled Substances Act, 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.

2.3. Requirements for studies conducted under an abbreviated IDE

2.3.1. You, or any person acting for or on behalf of you may not:

2.3.1.1. Promote or test market the investigational device, until after FDA has approved the device for commercial distribution.

2.3.1.2. Commercialize the investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

2.3.1.3. Unduly prolong the investigation.

2.3.1.4. Represent that the investigational device is safe or effective for the purposes for which it is being investigated.

2.3.2. If the study is investigator-initiated:

2.3.2.1. Label the device as follows:

2.3.2.1.1. The device or its immediate package must bear a label with the following information: the name and place of business of the manufacturer, packer, or distributor (in accordance with §801.1), the quantity of contents, if appropriate, and the following statement: “CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use.” The label or other labeling shall describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.

2.3.2.1.2. The device must not bear any statement that is false or misleading in any particular and shall not represent that the device is safe or effective for the purposes for which it is being investigated.

2.3.2.2. Comply with the requirements of 21 CFR §812.46 with respect to monitoring investigations.

2.3.2.3. Maintain 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).

2.3.2.4. Ensure that participating investigators maintain the records required by 21 CFR §812.140(a)(3)(i) and make the reports required under 21 CFR §812.150(a) (1), (2), (5), and (7).

2.3.3. Ensure that the 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 your care, and for the control of devices under investigation.

2.3.3.1. Ensure that informed consent is obtained in accordance with FDA regulations.

2.3.4. You may determine whether potential subjects would be interested in participating in an investigation, but do not request the written informed consent of any subject to participate, and do not allow any subject to participate before obtaining IRB and FDA approval.

2.3.5. Conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

2.3.6. Permit the investigational device to be used only with subjects under your supervision.

2.3.6.1. Do not supply an investigational device to any person not authorized under this part to receive it.

2.3.7. Disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required by FDA regulations.

2.3.7.1. Promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

2.3.8. Upon completion or termination of a clinical investigation or your 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.

2.3.9. Maintain the following accurate, complete, and current records relating to the your participation in an investigation:

2.3.9.1. Records of each subject's case history and exposure to the device. Case histories include:

2.3.9.1.1. The case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes

2.3.9.1.2. Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to

obtain informed consent. The case history for each individual must document that informed consent was obtained prior to participation in the study

2.3.9.2. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

2.3.9.3. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

2.3.10. Permit authorized FDA employees, at reasonable times and in a reasonable manner:

2.3.10.1. To enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

2.3.10.2. To inspect and copy all records relating to an investigation.

2.3.10.3. To inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by you to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

2.3.11. Prepare and submit the following complete, accurate, and timely reports:

2.3.11.1. Submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after you first learn of the effect.

2.3.11.2. Report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of your part of an investigation.

2.3.11.3. If you use a device without obtaining informed consent, report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

2.3.11.4. Upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

2.4. Expanded Access

2.4.1. FDA has an expanded access program, which allows the use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of expanded access is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

2.4.2. In all cases of expanded access, investigators are responsible for reporting adverse drug events to the sponsor, ensuring that the informed consent requirements of part 50 of this chapter are met, ensuring that IRB review of the expanded access use is obtained in a manner consistent with the requirements of part 56 of this chapter, and maintaining accurate

case histories and drug disposition records and retaining records in a manner consistent with the requirements of §312.62. Depending on the type of expanded access, other investigator responsibilities under subpart D may also apply.

2.5. Requirements for studies conducted under an IDE

2.5.1. You, or any person acting for or on behalf of you may not:

2.5.1.1. Promote or test market the investigational device, until after FDA has approved the device for commercial distribution.

2.5.1.2. Commercialize the investigational device by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling.

2.5.1.3. Unduly prolong the investigation.

2.5.1.4. Represent that the investigational device is safe or effective for the purposes for which it is being investigated.

2.5.2. Ensure that the 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 your care, and for the control of devices under investigation.

2.5.2.1. Ensure that informed consent is obtained in accordance with FDA regulations.

2.5.3. You may determine whether potential subjects would be interested in participating in an investigation, but do not request the written informed consent of any subject to participate, and do not allow any subject to participate before obtaining IRB and FDA approval.

2.5.4. Conduct the investigation in accordance with the signed agreement with the sponsor, the investigational plan, this part and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

2.5.5. Permit the investigational device to be used only with subjects under your supervision.

2.5.5.1. Do not supply an investigational device to any person not authorized under this part to receive it.

2.5.6. Disclose to the sponsor sufficient accurate financial information to allow the applicant to submit complete and accurate certification or disclosure statements required by FDA regulations.

2.5.6.1. Promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study.

2.5.7. Upon completion or termination of a clinical investigation or your 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.

2.5.8. Maintain the following accurate, complete, and current records relating to the your participation in an investigation:

2.5.8.1. All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports.

2.5.8.2. Records of receipt, use or disposition of a device that relate to:

2.5.8.2.1. The type and quantity of the device, the dates of its receipt, and the batch number or code mark

2.5.8.2.2. The names of all persons who received, used, or disposed of each device

2.5.8.2.3. Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of

2.5.8.3. Records of each subject's case history and exposure to the device. Case histories include:

2.5.8.3.1. The case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes.

2.5.8.3.2. Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual must document that informed consent was obtained prior to participation in the study.

2.5.8.3.3. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

2.5.8.3.4. A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

2.5.8.4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

2.5.8.5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

2.5.9. Permit authorized FDA employees, at reasonable times and in a reasonable manner:

2.5.9.1. To enter and inspect any establishment where devices are held (including any establishment where devices are manufactured, processed, packed, installed, used, or implanted or where records of results from use of devices are kept).

2.5.9.2. To inspect and copy all records relating to an investigation.
2.5.9.3. To inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by you to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

2.5.10. Prepare and submit the following complete, accurate, and timely reports:

2.5.10.1. Submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after you first learn of the effect.
2.5.10.2. Report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of your part of an investigation.
2.5.10.3. Submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
2.5.10.4. Notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency.

2.5.10.4.1. Give such notice as soon as possible, but in no event later than 5 working days after the emergency occurred.
2.5.10.4.2. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan.
2.5.10.4.3. If these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval of FDA and the IRB are required.

2.5.10.5. If you use a device without obtaining informed consent, report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
2.5.10.6. Within 3 months after termination or completion of the investigation or your part of the investigation, submit a final report to the sponsor and the reviewing IRB.
2.5.10.7. Upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

3. REFERENCES

3.1. 21 CFR §312.60, §312.61, §312.62, §312.64, §312.66, §312.68, §312.69, §312.300, §312.305, §812.40, §812.42, §812.43, §812.45, §812.46

1. PURPOSE

1.1. This guidance outlines the additional obligations of investigators conducting research subject to ICH-GCP.

2. GUIDANCE

2.1. Investigator's Qualifications and Agreements

2.1.1. The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB, and/or the regulatory authority(ies).

2.1.2. The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

2.1.3. The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

2.1.4. The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

2.1.5. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

2.2. Adequate Resources

2.2.1. The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

2.2.2. The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

2.2.3. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

2.2.4. The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

2.3. Medical Care of Trial Subjects

2.3.1. A qualified physician (or dentist, when appropriate), who is an investigator or a subinvestigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

2.3.2. During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

2.3.3. It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

2.3.4. Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

2.4. Communication with IRB

2.4.1. Before initiating a trial, the investigator/institution should have written and dated approval from the IRB for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

2.4.2. As part of the investigator's/institution's written application to the IRB, the investigator/institution should provide the IRB with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB.

2.4.3. During the trial the investigator/institution should provide to the IRB all documents subject to review.

2.5. Compliance with Protocol

2.5.1. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval by the IRB. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

2.5.2. The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

2.5.3. The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

2.5.4. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted: a) to the IRB for review and approval, b) to the sponsor for agreement and, if required, c) to the regulatory authority(ies).

2.6. Investigational Product(s)

2.6.1. Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

2.6.2. Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

2.6.3. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

2.6.4. The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

2.6.5. The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

2.6.6. The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

2.7. Randomization Procedures and Unblinding

2.7.1. The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

2.8. Informed Consent of Trial Subjects

2.8.1. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB's written approval of the written informed consent form and any other written information to be provided to subjects.

2.8.2. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject’s consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. The communication of this information should be documented.

2.8.3. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

2.8.4. None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

2.8.5. The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval by the IRB.

2.8.6. The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

2.8.7. Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

2.8.8. Prior to a subject’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

2.8.9. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

2.8.10. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

2.8.10.1. That the trial involves research
2.8.10.2. The purpose of the trial
2.8.10.3. The trial treatment(s) and the probability for random assignment to each treatment
2.8.10.4. The trial procedures to be followed, including all invasive procedures
2.8.10.5. The subject's responsibilities
2.8.10.6. Those aspects of the trial that are experimental
2.8.10.7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant
2.8.10.8. The reasonably expected benefits.

2.8.10.8.1. When there is no intended clinical benefit to the subject, the subject should be made aware of this

2.8.10.9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks
2.8.10.10. The compensation and/or treatment available to the subject in the event of trial-related injury
2.8.10.11. The anticipated prorated payment, if any, to the subject for participating in the trial
2.8.10.12. The anticipated expenses, if any, to the subject for participating in the trial
2.8.10.13. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled
2.8.10.14. That the monitor(s), the auditor(s), the IRB, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access
2.8.10.15. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available
2.8.10.16. If the results of the trial are published, the subject's identity will remain confidential That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes

available that may be relevant to the subject's willingness to continue participation in the trial

2.8.10.17. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury

2.8.10.18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated

2.8.10.19. The expected duration of the subject's participation in the trial

2.8.10.20. The approximate number of subjects involved in the trial

2.8.11. Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

2.8.12. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

2.8.12.1. Therapeutic trials (i.e. a trial in which there is anticipated direct clinical benefit to the subject) should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

2.8.13. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally. b) The foreseeable risks to the subjects are low. c) The negative impact on the subject's well-being is minimized and low. d) The trial is not prohibited by law. e) The approval of the IRB is expressly sought on the inclusion of such subjects, and the written approval covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

2.8.14. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval by the IRB, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

2.9. Records and Reports

2.9.1. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

2.9.2. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

2.9.3. Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be

maintained); this applies to both written and electronic changes or corrections. Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

2.9.4. The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

2.9.5. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

2.9.6. The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

2.9.7. Upon request of the monitor, auditor, IRB, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

2.10. Progress Reports

2.10.1. The investigator should submit written summaries of the trial status to the IRB annually, or more frequently, if requested by the IRB.

2.10.2. The investigator should promptly provide written reports to the sponsor, the IRB and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

2.11. Safety Reporting

2.11.1. All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB.

2.11.2. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

2.11.3. For reported deaths, the investigator should supply the sponsor and the IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

2.12. Premature Termination or Suspension of a Trial

2.12.1. If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

2.12.2. If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB, and should provide the sponsor and the IRB a detailed written explanation of the termination or suspension.

2.12.3. If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.

2.12.4. If the IRB terminates or suspends its approval of a trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

2.13. Final Report(s) by Investigator

2.13.1. Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

2.14. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP).

3. REFERENCES

3.1. ICH Topic E 6 (R1) Guideline for Good Clinical Practice, (CPMP/ICH/135/95)