

A Guide for Researchers

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Midlands Independent Review Board®
8417 Santa Fe Drive, Suite 100, Overland Park, KS 66212
Phone: 913.385.1414
www.mlirb.com • info@mlirb.com

The purpose of this guide is to provide you with information about MLIRB's processes. MLIRB will from time to time amend or update the guide. MLIRB 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.

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1. Introduction

Midlands Independent Review Board (MLIRB) is pleased to provide this handbook of information about using MLIRB 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 MLIRB

Midlands Independent Review Board (MLIRB) was founded in 2001 to meet the ethical review needs of the clinical trials industry to provide human subject protection.

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

In 2010, MLIRB became accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). In 2013, AAHRPP renewed MLIRB's accreditation status. MLIRB continues to be fully accredited.

MLIRB has worked with major pharmaceutical and device manufacturers, CROs, and the biotech industry.

Arsenal Capital Partners formed the WIRB Copernicus Group (WCG) and in 2014 acquired MLIRB. Arsenal Capital Partners is a leading New York-based private equity firm that invests in middle market healthcare, specialty industrial, and financial services companies.

MLIRB's position within the WIRB-Copernicus Group provides it access to nationally recognized experts and processes. MLIRB 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), New England IRB, Aspire IRB, Western IRB, and IRBNet, and through those relationships, we will leverage every opportunity to bring added value to you.

The WIRB Copernicus Group (WCG) continues to expand its offerings via new acquisitions and service lines – go to www.wcgclinical.com to find out the latest.

3. Working With MLIRB for IRB Review – An Overview

Midlands Independent Review Board is composed of one panel that meets twice a week.

If not eligible for expedited review, new protocols are assigned based on the next available panel meeting.

MLIRB 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 MyConnexus[®] account can access detailed tracking information and can download review documents from the site. Click on “LOGIN TO WCG MYCONNEXUS” link on the home screen of www.MLIRB.com to set up an account.

To learn more about accessing research review details on MLIRB’s web site, MLIRB’s panel structure, or to determine the panel assignment of a particular protocol, call MLIRB at 913-385-1414 or e-mail info@MLIRB.com.

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

Confidential Disclosure Agreements (CDAs) between sponsors and Midlands Independent Review Board (MLIRB) are not required by MLIRB. 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 MLIRB’s General Counsel for preparation.

4. Submitting Documents for MLIRB Review

A “smart” form is available for most MLIRB 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 MyConnexus” on the www.MLIRB.com home page to set up an account.

Submissions may be emailed to MLIRB at info@MLIRB.com. An email acknowledging the submission will be sent. The confirmation e-mail also serves as an official MLIRB acknowledgement of receipt. Documents submitted via MyConnexus[®] are also stored there for other users with access to your workspace to view.

5. Materials required for initial review

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

A. Items required for all initial review requests

- **Initial Review Submission Form** For best results, MLIRB recommends use of its smart submission forms
- **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.)
- **Curriculum Vitae (CV)** for Principal Investigator
- **Consent form** (If MLIRB 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 Approval letter; 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

A copy of each of the following is required:

- **Investigator's Drug Brochure**
- **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.**
- **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. WCG can provide IBC oversight; see the Review Services tab at www.WCGclinical.com.**

ii. If a DEVICE study, a device manual is required (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 HUD branch of our initial review submission form designed for such review requests. (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.)

6. Regulations Affecting Clinical Research, Including HIPAA

A. The Regulatory Framework Within Which MLIRB Functions

MLIRB is registered with FDA/OHRP. MLIRB’s IRB registration number is IRB00001486, and under the IORG number, MLIRB has 1 IRB registration number for the Board IRB00001931.

MLIRB reviews many types of human subject research, including clinical research, behavioral research, and epidemiological research, in the United States and internationally. MLIRB 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 MLIRB at info@MLIRB.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.

MLIRB has established written procedures that ensure that research approved by MLIRB meets these three primary standards. However, MLIRB 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, MLIRB reviews research funded by the Department of Defense, the Department of Education and other federal agencies.

B. HIPAA

MLIRB also provides services under the Privacy Rule (45 CFR Parts 160 and 164 of the Health Insurance Portability and Accountability Act of 1996). MLIRB will review requests for waivers of authorization and partial waivers of authorization for covered entities upon request (MLIRB forms for requesting review of partial and full waivers of authorization are available on the Download Forms page of www.MLIRB.com and are integrated into the Initial Review Smart Form available on the MLIRB website). MLIRB 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. MLIRB will review separate authorization documents upon request.

7. Conflicts of Interest

MLIRB 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,” MLIRB 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.MLIRB.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).]

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 MLIRB Board generally does not know investigators and other parties intimately enough to judge their integrity, MLIRB 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.

- 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.

8. The Informed Consent Process

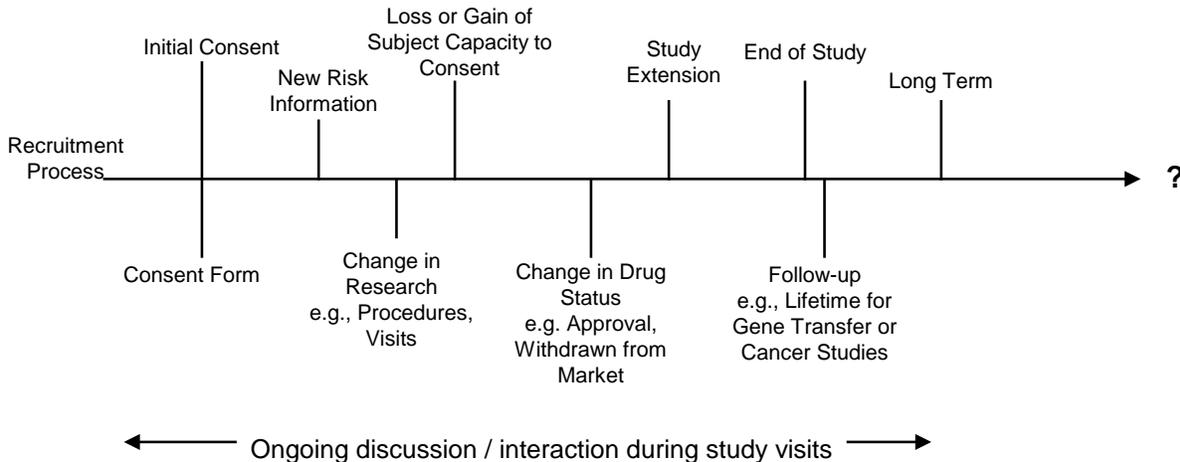
The informed consent process is central to the ethical conduct of research. It is an on-going conversation between the human research subject and the researchers that begins before consent is given and continues until the end of the subject's involvement in the research (see consent process diagram, 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.

- **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, **consent 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 subject 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.

MLIRB'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. MLIRB 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)

MLIRB 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.

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.

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

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. For more information refer to 21 CFR 50.23 (a)-(c).

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.

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, MLIRB 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.

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.

MLIRB 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.

i. Some general guidelines for writing a consent form

Consent templates and/or outlines are available from MLIRB, as well as from some NIH groups such as NCI, and other sources. See www.MLIRB.com 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 volunteer page 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 (MLIRB 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. MLIRB 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.

MLIRB 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.

MLIRB 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 MLIRB, please consider what method you will use to ensure that no subjects are enrolled unless the CTA and the MLIRB-approved consent form are in agreement.

Our Initial Review Submission form requires submitters agree to the following: Consistent with AAHRPP's requirements in connection with its accreditation of IRBs, the individual and/or organization submitting this form shall promptly communicate or provide, and where

necessary cause each investigator to promptly communicate or provide... 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.

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 MLIRB).

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

January 4, 2011 a rule for informed consent was announced in the Federal Register: (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.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."

Since this wording is only required for certain types of clinical trials, and only for those initiated on or after the compliance date, MLIRB does not automatically include the text in all existing and new consent forms.

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 MLIRB 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, MLIRB 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. MLIRB recommends providing a simple assent information sheet that explains the research to older children and adolescents.

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 (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~~ 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?

In March 2016, WCG announced the creation of the WCG Gene Therapy Advisory Board. Through the Board, our clients have access to the best and most current thinking in this new and emerging field. Go to www.wcgclinical.com for more information.

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. WCG is a leader in this area. MLIRB 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.

- **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.

- **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

- **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 MLIRB'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 consentor 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

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. MLIRB 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 MLIRB 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 Approval letter “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 MLIRB-approved consent form from the pregnant partner before any data collection can occur. If MLIRB has not approved a pregnant partner consent form for this protocol, MLIRB has a template consent that we can provide to you for this purpose. Please contact us if you have any questions.”

9. Suggested Guidelines for Writing a Research Protocol

If you will be drafting a protocol for submission to MLIRB, 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 MLIRB 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) 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.

10. Requirements for Human Subject Protection Training

MLIRB 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. Please note that HIPAA training or prior research experience alone does not satisfy this requirement for training in human subject protection. MLIRB'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. If your team has not completed training, please be sure an equivalent training has been completed and is listed in the submission.

When standard therapy is part of the research, MLIRB 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.

MLIRB 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 MLIRB.

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.)
- The NIH Office of Extramural Research provides an online tutorial called "Protecting Human Research Participants" <http://phrp.nihtraining.com/users/login.php>.

11. Suggested Guidelines for Evaluating Staff Levels at the Site

Our **initial review submission forms** ask for information about staffing levels at the site. MLIRB 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.

12. Compensation to Investigators for the Conduct of Research

Financial compensation to investigators should be at fair market value for the procedures and services provided. MLIRB 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)

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

MLIRB's **Investigator Request for Approval/Facility Description form** ask for information about an IND. As a general rule, MLIRB 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 MLIRB 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 MLIRB.

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

14. 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 MLIRB.

If the research is SR, provide MLIRB 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 MLIRB 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.

15. Special considerations for Behavioral Research

MLIRB 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.

16. Special considerations for Federally Funded Research

i. Grants

For federally funded research, MLIRB 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 MLIRB) 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 MLIRB is IRB00001931. MLIRB will request a copy of the DHHS-approved FWA application, but if it is not available, it is not required for review.
- 2) A sample IRB Authorization Agreement must be completed. The form is also available on the Download Forms page of www.MLIRB.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 MLIRB at info@mlirb.com for clarification or assistance regarding these requirements.

17. Special considerations for multi-center studies

Each individual submission for a multi-center study must be accompanied by a completed initial review submission form. We recommend using the "smart" form available from the Download Forms page of www.MLIRB.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.

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 MLIRB for information about submission requirements for specific types of research.

i. Consent forms for multi-center research

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

Site-specific information which must be provided on the MLIRB 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 1-617-243-3924 or check the My**Connexus**[®] page for that protocol (your sponsor or CRO contact can grant you access).

ii. Impact of changes

Investigators who provide instructions for use of an a consent form other than the one already approved by MLIRB 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 MLIRB, state in the submission that the items have been previously reviewed by MLIRB. 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

MLIRB 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 Approval letter (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 MLIRB to conduct a pre-review:

- Completed initial review submission form.
- 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
- 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.

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.

18. 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 MLIRB. MLIRB provides translations services for MLIRB-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. Our 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. MLIRB-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 MLIRB. The request should identify the Sponsor, Sponsor Protocol Number, Investigator, and the language requested. The subject cannot be enrolled until they have received the MLIRB-approved translated consent. If MLIRB is asked to provide a price quote for the translation, the translation process will not begin until MLIRB receives authorization to proceed.

MLIRB 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 (MLIRB requires written confirmation that the designee will accept the invoice).

MLIRB 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 MLIRB translation.

ii. Sponsor/CRO/Site Translations:

The MLIRB-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 MLIRB 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 MLIRB 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 MLIRB approved [name of document; such as, Research Subject Information and Consent Form, advertisement, for consents date or version number] for [sponsor / protocol number], [MLIRB protocol number] this _____ day of _____, *[month / year]*.

(Signature of Translator)

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

19. Special considerations for enrollment of wards of the state

Our 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.

20. 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 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)).

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.

21. IRB Transfer

An IRB transfer happens when a study that has been approved by another IRB is transferred to MLIRB. 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 MLIRB.

A. Required documentation for an IRB transfer review request:

- Initial Review Submission Form (available on the Download Forms page of www.MLIRB.com)
- Background information provided on the MLIRB **Hospital/University Waiver Form**
- A copy of the complete current protocol if not already on file at MLIRB

- 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 [Investigator Request for Approval/Facility Description](#) 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).

*MLIRB 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, MLIRB will provide the site with an updated consent form with instructions for how subjects can contact MLIRB if they have questions about their rights as a research subject or with questions, concerns, or complaints about the research. Alternatively, if the site’s subjects are all in “follow-up only” status, MLIRB 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.

22. 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 MLIRB 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 Approval letter (COA).

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

An Approval letter

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

Depending on the type and extent of the Board's changes, the consent form.

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. 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.

iv. 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 deferred item is brought back to the same panel that deferred 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.

Incomplete submissions and inaccurate information. If answers on the MLIRB 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.

v. Pull

The Board may “pull” an agenda item at the request of the submitter, MLIRB 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.

23. 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 MLIRB before being implemented, unless a serious safety concern requires immediate implementation by the investigator.

You may email MLIRB at info@mlirb.com 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 MLIRB-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 MLIRB-approved consent form**. In order to facilitate the submission of consent form changes, MLIRB now routinely provides sponsors and CROs with a clean copy of each MLIRB-approved consent (without site specific information in it).

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

ii. How to submit a consent form modification

Requests for consent form modifications should consist of an e-mail submission to info@mlirb.com and a copy of the MLIRB-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 MLIRB-

approved consent form. In order to facilitate the submission of consent form changes, MLIRB now routinely provides sponsors and CROs with a clean copy of each MLIRB-approved consent (without site specific information in it). Changes sent to MLIRB on the *sponsor's* template consent form will not be accepted.

MLIRB 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 MLIRB's electronic workflow system.

In general, a statement justifying changes is very helpful and can reduce the need for MLIRB 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.

Documents submitted for review can also be uploaded securely from the MLIRB web site, mailed, or e-mailed (info@MLIRB.com). Submissions should reference the sponsor protocol number and/or MLIRB 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 MLIRB for another site. If you agree to accept the changes already approved, your review will take place more quickly. You can contact MLIRB Client Services to determine if pre-approved language exists for your change in research.

iii. 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, MLIRB 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 our **Investigator Request for Approval/Facility Description Form**, license, and CV for the new investigator (unless current versions are already on file with MLIRB), 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 MLIRB 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).

iv. 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 MLIRB protocol and study numbers.

24. Additional changes which require submission to MLIRB

- Notify MLIRB 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 MLIRB [Investigator](#) Request for Approval/Facility Description Form for each new or updated location and forward to us.
- Notify MLIRB 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 MLIRB 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 MLIRB. If you are in doubt about submitting a particular item, call MLIRB at 1-913-385-1414 or e-mail info@MLIRB.com.

25. Subject Recruitment Materials (Ads, etc.)

E-mail MLIRB at info@mlirb.com to submit advertisements for review after initial review of the research. 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.

MLIRB 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 MLIRB 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 MLIRB, state in the cover letter or e-mail that the items have been previously reviewed by MLIRB. MLIRB 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:

To avoid unnecessary additional production costs due to re-work, it is strongly recommended that MLIRB 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 MLIRB for review, MLIRB 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 MLIRB for final approval before use with subjects and **MUST** match the MLIRB approved script. Submit a copy of the corresponding script when you send the recording to MLIRB 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.

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: MLIRB 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, MLIRB 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 MLIRB 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 MLIRB 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 MLIRB has approved it.

Only content pertaining to research needs to be reviewed by the IRB; submit to MLIRB only website content which provides information to potential subjects about research participation, as well as information about specific studies that MLIRB 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.

MLIRB 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 MLIRB receives a request to close the file.

Doctor to Doctor Materials, Press Releases: 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, MLIRB does not require prior IRB review of doctor-to-doctor letters, press releases, or interviews with the media and there is no need to provide MLIRB

with copies of these materials. However, if you would like to have IRB review for such materials we will provide a review upon submission.

26. MLIRB Requirements for Screening Materials

The Board recommends that submitted screening materials should conform to the following guidelines:

Introductory Statement:

- The screening script should 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 should not describe the type of questions that will be asked as “confidential;” e.g., 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 should 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 should include a closing statement informing the subject of whether or not they have met the preliminary screening requirements.
- The script should 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 should be in language understandable by lay people. If complicated medical terms must be included in the screening script, please provide MLIRB with an explanation of how they will be explained to the subjects.
- MLIRB realizes that the script may not be followed verbatim, as subjects may ask additional questions or stray from the topic. This is acceptable, but MLIRB expects that the interviewer will keep as closely as possible to the spirit and letter of the script.
- It is useful to MLIRB if the investigator informs MLIRB 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.

27. 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.

MLIRB 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.

28. Generic Advertisements

MLIRB 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.

29. Expiration and Renewal of Generic Materials

Approved generic items are generally valid for one year. When the anniversary date approaches, MLIRB staff will contact the submitter and inquire if renewal is desired. MLIRB 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 MLIRB 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.

30. MLIRB reporting requirements

A. "Promptly Reportable Information" form

Use the MLIRB 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 MLIRB.

MLIRB discontinued asking research sites to determine if an event constituted an “unanticipated problem” as defined by the regulations; instead, MLIRB create a new, easier to use, single Promptly Reportable Information form that provides sites with categories of information to report to MLIRB 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 MLIRB 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 MLIRB as a change in research for federally funded research and FDA drug and biologic studies. 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 MLIRB 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 MLIRB 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).

31. Overview of MLIRB’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 not less than once per year [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 may also direct more frequent than annual review for other research as deemed appropriate.

i. Site Reporting:

Completed Investigator Summary Report provide MLIRB with the study-related data necessary to monitor the progress of the research at sites. Identifying information including investigator name, sponsor name, and protocol number is listed at the top of each form. The Investigator Summary Report is sent out approximately 50 days before the study’s expiration date, in order to ensure it is completed and sent back to MLIRB 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.

Investigator Summary Report forms must be filled out completely and returned to MLIRB in a timely manner. Even if the site has not started enrolling subjects, the site must complete the Investigator Summary Report form and return it to MLIRB before the due date printed on on the letter to site, to inform the Board of the study’s status at the site.

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

ii. Sponsor Reporting:

Before each annual review, MLIRB sends out a Sponsor/CRO Information Form to the sponsor or CRO contact we have on file. The Sponsor/CRO Information Form 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 Sponsor/CRO Information Form before the due date indicated in the notification document. The individual study sites will continue to receive separate site Investigator Summary Report forms to complete and submit as well.

We want to make the Sponsor/CRO Information Form process as efficient as possible for all parties. Therefore, MLIRB will accept receipt of the completed Sponsor/CRO Information 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. MLIRB 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 Sponsor/CRO Information Form is sent out approximately 50 days before the protocol’s expiration date, in order to ensure it is completed and sent back to MLIRB before the Board conducts the continuing review of the study. The Board may take action to suspend or terminate approval of the research if a report is not accurately completed and returned promptly.

iii. Delinquent Progress Reports (Site Investigator Summary Reports and Sponsor/CRO Information Form)

If a completed report is not returned to MLIRB in a timely manner, MLIRB 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 MLIRB 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.

1. MLIRB will continue to follow-up with the investigators, sponsors and CRO contacts to facilitate timely receipt of a continuing review report. If no response is received within 20 days of the expiration date the delinquency is reported to the Board. If the Board

suspends the research, MLIRB 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 MLIRB 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 MLIRB.

iv. Definition of Screen Failures and Withdrawals

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

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: A subject is considered to have been withdrawn/discontinued from the research when the subject either stopped participation or the research team stopped the subject's participation early for reasons other than reaching a study endpoint. Do not count screen failures when reporting withdrawals to MLIRB.

v. Study Renewal

Sites receive a MLIRB Investigator Summary Report form when the expiration date is approaching. The Board may conduct the study continuing review up to 30 days prior to the expiration date listed on the Approval letter. **Review fees apply for the continuing review service** and review is carried out unless MLIRB receives a study closure notice *prior to the Board's renewal review*. If a closure notice is received by MLIRB before the expiration date, but after the Board's continuing review, the site is still billed for the renewal review. To avoid unnecessary reviews and fees, do not delay reporting a study closure to MLIRB 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 the continuing review for an additional review period, a Approval letter is forwarded to the investigator and other study contacts as applicable. 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 Approval letter will indicate approval of a consent form and will be accompanied by a revised consent form.

32. Study Closure

MLIRB considers the study open at a site until a study closure report is received. An Investigator Summary Report form 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.

MLIRB will close the study upon receipt of the Investigator Summary Report form. A MLIRB **Investigator Summary Report** form is available at www.MLIRB.com.

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

33. 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)).

MLIRB conducts the following types of site visits:

- For-Cause – MLIRB staff initiate “for-cause” site visits in response to concerns raised about the site, investigator, etc. These visits are usually carried out by WIRB-Copernicus Group (WCG) Regional Representatives, MLIRB Board members or MLIRB 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-Copernicus Group (WCG) Regional Representatives, MLIRB Board members or MLIRB management.
- Visits to Massachusetts Investigators – The Commonwealth of Massachusetts requires an on-site visit by a MLIRB 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 MLIRB site visit, please consult the current fee schedule.

MLIRB reviews all site visit reports. If any follow-up is required, the investigator will be informed about the Board’s decision.

34. Fees

MLIRB 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 MLIRB at 1-913-385-1414 or info@MLIRB.com.

Research Review fees at MLIRB fall into four general categories:

1. **Initial Review of the research.** Initial review encompasses the review of the research protocol, one 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. The review for an investigative site is an additional fee.

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 Continuing 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 MLIRB. The change in research fee applies each time board review and preparation of regulatory documentation is required for a research site.
4. **Miscellaneous.** MLIRB bills additional fees for services such as translations and acknowledgements.

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.

35. Reconsiderations

In accord with 21 CFR §56.109(e) and 45 CFR §46.109(d), MLIRB 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 MLIRB 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 MLIRB and ask for a reconsideration; however, we advise you not to delay complying with the Board's instructions.