A guide to partnering with CGIRB in the protection of human subjects taking part in research

Investigator Guidebook

copernicus group independent review board

A WIRB-Copernicus Group Company

CGIRB CONTACT INFORMATION

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For Priority Processing use Connexus® to make all submissions

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I. INTRODUCTION

As the principal investigator (PI), the health and welfare of all human research subjects at your site is your responsibility. This Guidebook contains valuable information that will outline your responsibilities to protect research subjects while complying with local, state, and federal regulations and guidelines regarding the conduct of clinical studies. Please take time to carefully read the enclosed information and ask your sub-investigators and staff to do the same.

About Copernicus Group IRB

Copernicus Group IRB (CGIRB) was established in 1996, and consists of an independent institutional review board (CGIRB Board) and support staff. CGIRB provides ethical review and support services to principal investigators (PIs), institutions, contract research organizations (CROs), and sponsors of human subjects' research.

In 2004, CGIRB was awarded full accreditation of the human research protection program by AAHRPP®, the Association for the Accreditation of Human Research Protection Programs, Inc. CGIRB is registered with the Office for Human Research Protections (OHRP) and FDA as **IRB00001313**. Our current effective date is available at the OHRP website: http://ohrp.cit.nih.gov/search/.

The CGIRB Board approval is based on CGIRB's determination that all regulatory requirements for approval have been met. The CGIRB Board expects the PI to ensure the research study is conducted in compliance with all federal, state, and local requirements governing human subject research, as well as the requirements of CGIRB.

CGIRB reviews research in accordance with three primary standards, as well as other regulatory standards, when appropriate:

- *The Food and Drug Administration (FDA) Regulations, Protection of Human Subjects (21 CFR 50) and Institutional Review Boards (21 CFR 56)*
- *The Health and Human Services (HHS) Regulations, Protection of Human Subjects (45 CFR 46 Subparts A, B, C, and D)*
- *The International Conference on Harmonization (ICH) "Guidance for Industry, E6 Good Clinical Practices: Consolidated Guidance*

The CGIRB Board reviews research protocols and study related information, as well as investigator qualifications and resources to assure regulatory compliance. Please see CGIRB's full Compliance Statement on our website.

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, consult the OHRP web site, or contact CGIRB's Client Services.

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.

CGIRB abides by the federal regulations that pertain to research conduct, but also may exceed these requirements in some areas. Please familiarize yourself and your staff with our written policies and procedures (summarized in this Guidebook and available at *www.cgirb.com*) so that we can work together to better protect human subjects.

If you have any questions, please contact us toll-free at +1 (888) 303-2224 (accessible from Puerto Rico as well). CGIRB's business hours are 8:00 AM to 5:00 PM (Eastern Time).

Also, be sure to visit our website at *www.cgirb.com* for our most current forms, additional information, and links to other resources for information regarding human subject protection. This site is updated frequently, so visit regularly.

We look forward to working with you to ensure the best protection possible for human subjects taking part in research at your site.

II. PRINCIPAL INVESTIGATOR OBLIGATIONS

A. Principal Investigator (PI) Obligations for Studies Under CGIRB Approval

This list of obligations is derived from Form FDA 1572 and from information contained within ICH GCP, the Belmont Report, 21 CFR, and 45 CFR. For more information on GCP or human subject protection training as well as guidelines for the conduct of research studies check www.fda.gov or http://www.hhs.gov/ohrp or the investigator section of our website: http://www.cgirb.com/investigators/.

According to the Code of Federal Regulations, you, as PI, are responsible for ensuring that the research study is conducted according to the protocol and in compliance with applicable regulations, for assuring that human subjects are protected, and for controlling any investigational product being used during the study. By signing on as a principal investigator for a human research study, you agree to:

1. Protect the rights, safety, and welfare of the human research subjects, in accordance with the Belmont Report and other guidance on protection of human subjects.
2. Not commence research activities until receipt of the IRB approval letter.
    a. There is an additional requirement for FDA-regulated research under an IND/IDE. Research activities (including recruitment) may not begin until either the IND/IDE is formally approved by the FDA or the 30-day review period passes with no FDA communication to hold study activities.
3. Conduct the study in compliance with the CGIRB-approved study protocol and applicable regulations and guidelines governing the conduct of clinical studies, including state and local laws and CGIRB policies and procedures. This includes

understanding and applying the definitions of legally authorized representative (LAR) and guardian in your state.

4. Provide evidence of your qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB, or the regulatory authority.

5. Delegate significant study-related duties only to qualified personnel, directly oversee these personnel to ensure that they are performing their duties in compliance with applicable standards and in the best interest of the human subjects, and maintain a list of these qualified persons to whom you have delegated these significant clinical trial-related duties.

    a. Where allowed or required, you may assign some or all duties for investigational articles accountability at your site to an appropriate pharmacist or another appropriate individual who is under your supervision.

    b. You, the pharmacist, or other designated individual will maintain records of the products' delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects. You should maintain records that document that the subjects are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

6. Ensure that there are adequate resources to carry out the research safely

7. Use only the informed consent form (ICF) and HIPAA authorization language approved by CGIRB. Any change to the consent/authorization document must be reviewed and approved by the CGIRB Board **prior** to use. Information (such as site address or compensation) submitted on the **Initial Review Submission** form is utilized to format an initial site-specific informed consent document. If the site is requesting site-specific wording to its ICF, other than site phone number, address, and subject compensation, the changes must be tracked and submitted on the CGIRB-approved template for the study.

8. Protect the privacy of the study subjects and maintain the confidentiality of the personal health information and study data. In determining if the level of privacy is sufficient, you should consider the degree of privacy of any information being collected and whether a reasonable person would consider the release of the information without permission to be an invasion of privacy. You should consider whether the provisions to maintain confidentiality are reasonable in relation to the degree of privacy of the information.

9. Obtain the legally effective informed consent of the subject or the subject's LAR/guardian prior to participation in the research.

    a. Ensure the circumstances of the consent process provide the prospective subject or the LAR/guardian sufficient opportunity to review the consent document and to consider whether to participate.

b. Ensure the circumstances of the consent process minimize the possibility of coercion or undue influence.

c. Ensure the individuals communicating information to the subject or the LAR/guardian during the consent process will provide that information in language that is understandable to the subject or the LAR/guardian.

d. Assess whether the subject or LAR/guardian comprehends the content of the ICF document.

e. Obtain assent from children or adult subjects unable to provide consent, when applicable.

f. Provide non-English speaking subjects with a CGIRB-approved translation of the ICF in the subject's primary language.

g. Ensure an impartial witness is included in the consent process when subjects or LARs/guardians are unable to read or are visually impaired, or when required by law.

10. Provide CGIRB with copies of all study-related materials that will be provided to subjects. The IRB may have already approved some documents submitted by the Sponsor to be used study-wide. These documents do not have to be separately submitted by the investigator.
11. Supervise the administration of the investigational product (IP) to the research subjects, as applicable, and maintain full accountability of the IP. This includes being familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the Sponsor.
12. Obtain CGIRB approval for any amendments to the protocol **prior** to implementation of the changes.
13. Promptly report to CGIRB all changes made to the research without CGIRB approval to eliminate an apparent immediate hazard to subjects.
14. Provide written reports to the Sponsor and CGIRB on any changes that significantly affect the conduct of the clinical trial or increase the risk to subjects.
15. Promptly report to CGIRB all unanticipated problems involving risks to research subjects or others.
16. Submit and obtain CGIRB approval for all advertisements and other subject recruitment or retention materials **prior** to use.
17. Provide Continuing Review Status Report and Principal Investigator Site Closeout Report information to CGIRB in the timeframe required by CGIRB.
18. Maintain and retain study-related documentation in accordance with applicable regulatory requirements.
19. Provide all the disclosures and follow the requirements pertaining to consent covered by ICH-GCP.

B. Study Conduct

As the PI, you agree to conduct the research study per the CGIRB-approved protocol and in compliance with all applicable federal, state, and local laws; Good Clinical Practice (GCP) guidelines; and the applicable CGIRB policies and procedures. The best interests and the safety of study subjects should be your primary concern. Subjects should be enrolled into the study equitably and with fair distribution. During and following a subject's participation in a clinical trial, the Investigator ensures that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the clinical trial.

C. GCP Training

Good Clinical Practice (GCP) is the international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. There are a number of various GCP training programs now available for you and your staff if you need additional information. These programs are offered in seminar and web-based formats. As PI, your responsibilities and obligations are fully detailed in Title 21 of the Code of Federal Regulations (21 CFR Parts 50, 54, 312, 812) and Title 45 CFR 46, the International Conference on Harmonization Consolidated Guidelines for GCP (ICH GCP or ICH E6). Additionally, there may be other regulations and guidelines affecting clinical research that you should be aware of, such as the Privacy Rule set forth in HIPAA (the Health Insurance Portability and Accountability Act) and any state or local requirements governing the conduct of research. Your obligations as the PI of a CGIRB-approved research project are summarized below.

Ensure that you and your staff have had appropriate training in properly conducting research involving human subjects and that each is aware of the specific obligations to communicate with the sponsor and CGIRB during the study.

D. Consent Process

The informed consent process is an important way to ensure the ethical principle of “respect for persons” is met, as specified in the Belmont Report. Ensure that an adequate informed consent process is conducted with each potential subject by minimizing the possibility of undue influence or coercion. Encourage the subject or LAR/guardian to take sufficient time to review the ICF and to ask questions regarding the research study, and give a clear and thoughtful answer to each question. Make sure to allow adequate time for the subject or LAR/guardian to understand the study expectations and consider whether to take part. Assess whether the subject or LAR/guardian comprehends the content of the ICF document.

Time spent on the informed consent process should be sufficient to allow the subject or LAR/guardian to read, understand, and ask questions about the study. Also be sure that you know what constitutes an LAR and/or guardian in your state. If you have questions about your state’s requirements for LARs and/or guardians, you should consult with an attorney and/or ask the sponsor for guidance. As the PI, it is your responsibility to ensure that any state and/or local requirements are incorporated in your site-specific ICF document.

Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, the Investigator makes a reasonable effort to ascertain the reason, while fully respecting the subject's rights.

1. Assent for minors and adults unable to consent

   CGIRB will communicate assent requirements, if any, as determined by the IRB on a study by study basis. Generally, conducting research involving minors and/or adult subjects who are legally unable to consent on their own behalf requires the permission of the parent(s)/guardian(s) or consent of the LARs, respectively. Assent of the subject also is required when the subject can understand his/her role as a research subject. Commonly , assent is appropriate from age ten up to the age of majority – usually 18 years (the age of majority is determined on the state level – it is your responsibility to comply with your state's requirements regarding the age of consent).

   The assent process should take into account the subject's experience and level of understanding in both discussion and written form. It should convey the basic information regarding the subject's participation in the study to enable the subject to make a decision about taking part in the research.

   Note: *You may need to obtain documented informed consent from a minor who reaches the age of majority during the study, or from an adult who regains decision-making capacity during the study.*

2. Translated Informed Consent Form and Other Documents

   In accordance with federal regulations and CGP Guidelines, ICF documents should be in language that is understandable to the subject and/or to the subject's LAR/guardian. When a non-English speaking subject is considering taking part in the study (or a non-English-speaking LAR/guardian is involved when the subject cannot consent on his/her own behalf), a CGIRB-approved translation of the ICF should be presented to the potential subject or LAR/guardian.

   In addition, it is always preferable that someone fluent in the subject's language conducts the informed consent discussion and is available throughout the research study to facilitate communication with the subject. As the PI for the study, it is your responsibility to inform CGIRB of the need for a translated ICF document.

   Approved certified translations of the ICFs can be obtained in one of the following ways:

   a. The investigator may ask CGIRB to provide an ICF translation in the desired language to be included in the review and approval of the research project. This may require approval from the Sponsor/CRO.

   b. The investigator or sponsor may facilitate the translation of an ICF document that has been approved by CGIRB for the study. CGIRB requires all ICF translations facilitated by investigators or sponsors to be performed by a certified translator to assure it is an accurate and complete translation of the English original. The investigator or sponsor must submit the translated document in Microsoft Word format, along with the Certificate of Translation, to CGIRB for consideration for approval prior to use.

In addition to the ICF, the HIPAA authorization language and any other documentation provided to study subjects (e.g., diaries, questionnaires) should be provided in language that is understandable to the subject or LAR/guardian. The process for obtaining a translation of these documents is the same as that described above for the ICF document.

A **Translation Request Form** must be submitted to CGIRB for all translation submissions, whether initiating a request with the IRB or submitting already translated documents for approval.

Please note:

- If a site deviates from the ICF template wording, that site will require a separate translation and a separate Certificate of Translation. The same is true for any site with site specific changes to their ICF.
- CGIRB does not require Back Translations for approval of the translated documents.
- Please submit a Translation Request Form with all translation submissions.

3. Exculpatory language

It is your responsibility as the principal investigator to ensure the information being communicated to the subject or the LAR/guardian during the consent process does not include exculpatory language through which the subject or the LAR/guardian is made to waive or appear to waive any of the subject's legal rights, or language through which the subject or the LAR/guardian releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

4. Waiver or Alteration of Consent

a. Waiver of Documentation of Informed Consent

i. The CGIRB Board may determine that written documentation of consent can be waived if:

1. The only record linking the subject and the research is the consent document.
2. The principal risk is potential harm resulting from a breach of confidentiality.
3. Each subject will be asked whether he or she wants documentation linking the subject with the research, and the subject's wishes will govern.
4. The research is not FDA-regulated.

ii. The CGIRB Board may determine that the requirement to obtain written documentation of the consent process can be waived if:

1. The research presents no more than minimal risk of harm to subjects.
2. The research involves no procedures for which written document of the consent process is normally required outside of the research context.

3. This waiver may be used in FDA-regulated research.

iii. If the CGIRB Board considers waiving the requirement to obtain written documentation of the consent process, a written description of the information that will be provided to subjects is reviewed.

iv. The CGIRB Board may require the investigator to provide subjects with a written statement regarding the research.

b. Waiver/Alteration of Elements of Informed Consent

i. For non-FDA-regulated studies, the CGIRB Board may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in the applicable regulations, or waive the requirements to obtain informed consent provided that the CGIRB Board finds that:

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; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

ii. The CGIRB Board may determine whether parental permission can be waived by determining that:

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

iii. The CGIRB Board may determine whether parental permission can be waived by determining that:

1. The research is designed for conditions or for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects.
2. An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted.
3. The research is not FDA-regulated

E. Protection of Subject Privacy and Data Confidentiality

As PI, you need to ensure that there is adequate protection of subject privacy and confidentiality of data at your site.

1. Privacy deals with the protection of the subjects themselves as individuals who deserve respect and autonomy. Protection of subject privacy refers to people and limiting unauthorized individuals' access to the actual person (not their identifiers or data).
2. Confidentiality refers to data (particularly personal health information) and procedures to limit unauthorized access to those data.

You should consider how you will protect **subject privacy**, such as assuring that the setting in which the consent process takes place is private and does not stigmatize the subject. You are responsible for assuring privacy during subsequent study visits and procedures as well.

To ensure **confidentiality of data**, you will want to address issues such as how you will store and retain your medical and research files and who will have access to your computer database. Ways that you can address confidentiality issues may include keeping subject identifiers and data in a locked cabinet with access limited to study personnel, password-protection of computer files and study-specific information and/or proper disposition of study records per a retention policy that adheres to federal regulations. Personal health information (PHI) should be disclosed only to those parties who have written authorization.

In determining if the level of privacy is sufficient, you should consider the degree of privacy of any information being collected and whether a reasonable person would consider the release of the information without permission to be an invasion of privacy. You should consider whether the provisions to maintain confidentiality are reasonable in relation to the degree of privacy of the information.

F. 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.

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 https://humansubjects.nih.gov/coc/apply, but NIH is not the only source for one, as several federal agencies issue certificates.

G. Record Keeping

In accordance with the applicable regulations and guidelines, it is your responsibility to maintain complete and accurate source documentation for each research subject as well as the essential study regulatory documents. Source documents may include progress notes, medical records, laboratory reports, test results (e.g., EKGs, X-rays), and other support data entered on the case report forms (CRFs), as applicable. Good documentation practices should be employed on all study-related documentation to assure the integrity of the data and to provide for a clear audit trail. Although a subject is not obliged to give his or her reasons for withdrawing prematurely from a clinical trial, you should make a reasonable effort to document the reason, while fully respecting the subject's rights.

When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remain part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed. You may ask a subject who is withdrawing whether he/she wishes to provide continued follow-up and further data collection subsequent to the withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject would distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through noninvasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

You must obtain the subject's informed consent for this described in the original informed consent form. CGIRB must approve the consent document prior to use. If a subject withdraws from the interventional portion of a study and does not consent to continued follow up of associated clinical outcome information, you must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, you may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival statuses.

The study records must be available for review by CGIRB and applicable regulatory agencies during the study and throughout the required retention period. You should contact the sponsor if you have questions about the records-retention requirements for a particular study.

H. Investigator 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)). Therefore, CGIRB reserves the right to visit your site as needed. CGIRB conducts the following types of visits:

- Routine – CGIRB may conduct routine audits of sites to review study documentation and evaluate investigator compliance with federal regulations, state and local laws, and CGIRB expectations as outlined in this Investigator Guidebook.
- Board-Directed – The Board directs site visits in response to observations or concerns raised about the site or investigator.

During the visit the CGIRB site visitor will review all relevant study documentation with respect to subject safety and regulatory compliance.

Massachusetts Investigators: Massachusetts Department of Public Health Regulations (105 CMR 700.009 (G)(2)(a) and MGLc 94C § 8) investigator site visits are required annually for FDA-regulated studies involving investigational drugs or biologics that are being conducted within the state of Massachusetts. A site visit is not required for studies involving investigational devices, however a routine investigator site visit may be conducted according to the criteria listed above. Massachusetts investigators may contact the Massachusetts Department of Public Health at 617.983.6712 for further information regarding the conduct of clinical research in Massachusetts.

I. Audits and Inspections

In accordance with federal regulations, study records must be available for review by CGIRB and applicable regulatory agencies during the study and throughout the required retention period. You should be prepared at any time for an audit/inspection by regulatory agencies, the sponsor, sponsor representatives, or CGIRB.

Regulatory inspections that result in written findings (e.g., issuance of a Form FDA 483 during an FDA inspection, receipt of a Warning Letter or Untitled Letters must be reported promptly to CGIRB. The reporting requirements and timelines are as follows:

1. Inspections of studies for which CGIRB is the IRB of record:
    a. Submit an un-redacted copy of the Form FDA 483/written findings to CGIRB within 5 business days of the close of the inspection or of receipt of a Warning Letter or Untitled Letter.
    b. Within 30 business days from the close of the inspection (or receipt of the letter), submit an un-redacted copy of any written responses you provided to the regulatory body addressing corrective and preventative measures taken or to be taken to remediate the noted problems.
    c. Response to the written response provided to FDA.
2. Inspections of studies for which CGIRB is **not** the IRB of record:
    a. Submit a copy (may be redacted) of the Form FDA 483/written findings to CGIRB within 30 business days of the close of the inspection, or within 30 days of receipt of a Warning Letter or Untitled Letter. Include in this submission copies of any written responses you provided by you or your site to the regulatory body addressing corrective and preventative measures taken or to be taken to remediate the noted problems.

If a regulatory inspection does not result in written findings a copy of the establishment inspection report (EIR) should be forwarded to CGIRB.

J. Financial Disclosures

CGIRB considers that the most important step in managing potential financial 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. The CGIRB initial review submission forms contain a section for reporting of financial conflicts of interest.

If any of the following are true for the PI, PI's immediate family (spouse and dependent children), the staff, or the staff's immediate family, CGIRB's Conflict of Interest Disclosure Form for Investigative Sites must be submitted.

- Has a financial interest in the research with value that cannot be readily determined (for example, stock that is 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 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 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 requires the investigator believes may interfere with his or her ability to protect subjects
- Is affiliated with an institution with a lower conflict of interest

Remember, this is not a one-time assessment. As the PI, it is your responsibility to re-assess for conflict of interest throughout the study. **If conflict of interest becomes an issue it must be reported to CGIRB immediately on CGIRB's Conflict of Interest Disclosure Form for Investigative Sites**. (See also, the Referral Fees, Incentives, and Bonus Payments section below).

K. Referral Fees, Incentives, and Bonus Payments

CGIRB does not allow referral fees for medical professionals or research staff (offering or accepting payment for referring patients to research studies, sometimes referred to as "finder's fees"). 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. Payments to subjects for referring others may be considered by the Board on a case-by-case basis and is generally allowable.

CGIRB has concerns that these practices may create a conflict of interest that has the potential to influence the selection of subjects and thus may increase research risks to subjects. Therefore, investigators should inform CGIRB when these situations arise. CGIRB will review the proposed incentive program to determine if the potential conflict of interests may be managed.

The investigator should report the use of planned recruitment bonuses or additional incentives, gifts or bonus payments to investigator or study staff beyond the original negotiated grant amount to CGIRB, as applicable.

CGIRB defines a recruitment bonus as an additional payment or incentive provided to the investigator or staff dependent solely on a particular number of subjects being enrolled, or dependent on the speed at which subjects are enrolled. The term "payment or incentive" includes any items of value, such as direct payment, gift certificates, travel vouchers, and so forth. Additional payments for additional work performed by staff in order to identify potential eligible study participants may be allowed on a case-by-case basis.

III. SUBMISSIONS TO CGIRB

Copernicus Group IRB typically meets four times a week to conduct review of items that require review by the convened Board. Incomplete packets or packets received after the submission deadline will be placed on a later meeting agenda. To access our meeting schedule, with corresponding submission deadlines, please reference the Board Meeting Schedule

In order to most efficiently initiate the initial review process, CGIRB prefers to receive documents electronically.

Electronic submissions can be made through Connexus®. Connexus provides clients and investigators with secure online access to all files and forms, including a comprehensive archive of study documents and prior submissions. This fully validated and 21 CFR Part 11 compliant system provides the ability to upload documents, access status tracking updates, assist in continuing review coordination and retrieve all previous study information. You can invite team members and study coordinators at your sites to join study-specific workspaces.

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

Forms are provided on the CGIRB website. Please check with your sponsor contact to determine what you need to submit directly to CGIRB. A review cannot be performed prior to the receipt of all appropriate information.

A. Review of Investigators

Investigators must obtain IRB approval before research can be conducted at a site. CGIRB reviews investigator qualifications separately from the protocol and considers additions of investigators to a protocol to be a minor modification to previously approved research.

Please note that this model of the investigator being approved separately from the protocol is the same for single-site or investigator-initiated applications. Therefore, even if a protocol for a single site study is approved by the IRB, the investigator must receive a separate IRB investigator approval letter prior to beginning study activities

Investigators must submit the following documents to the IRB to be considered for approval:

1. CGIRB's **Initial Review Submission** Form for the primary site where subjects will be seen.
2. CV for the PI that must show affiliation to at least one of the research site addresses where subjects will be seen. (Note: CGIRB does not require the submission of sub-investigator CVs, but does require a summary of qualifications for any research staff that will be participating in the conduct of the research.) PIs may submit sub-investigator CVs in place of a summary, if preferred.
3. If the PI is from Massachusetts, a copy of his/her research license is also required (Controlled Substance License).
4. Any site-specific advertisements. Such advertisements must be "clean" copies without any handwritten changes from the sponsor/CRO or site. Advertisements must be IRB approved prior to use in a given study.
5. **IRB Reliance Agreement** form (also commonly referenced as a Transfer of IRB Obligations or IRB Authorization Agreement) if the investigator is part of an institution or organization where a local IRB would have jurisdiction of the research site
6. If the site is requesting site-specific wording to its ICF, other than site phone number, address, and subject compensation, the changes must be tracked and submitted on the CGIRB-approved template for the study.

Other Principal Investigator Information, if applicable

Other Principal Investigator information that should be submitted to CGIRB:

1. If the site or PI was inspected/evaluated by any regulatory agency (e.g., FDA or OHRP) within the past five years and received a Form FDA 483 or other list of observations, CGIRB requires a copy of this documentation along with the site or PI's response(s) to the inspection observations.
2. If the site or PI was ever issued any of the following, CGIRB requires copies of all related documentation:
   - Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
   - Suspension
   - FDA Warning Letter
3. CGIRB requires copies of all related documents if any of the following have been denied, revoked, suspended, reduced, limited, placed on probation, not renewed, relinquished, or subject to disciplinary action for the PI:

- Research privileges at the site
- Medical licensure in any state
- Other professional licensure/registration
- Membership on any hospital staff
- Clinical privileges
- Professional society memberships or fellowship/board certifications

4. CGIRB requires all related documents if the PI has had any of the following:
   - A professional sanction, including fines, or Drug Enforcement Agency (DEA) prescribing
   - Privileges levied against the PI
   - Any patient or subject complaint against the PI, sub-investigator(s), or the research site (subject identifiers may be removed)
   - Any action or investigation currently pending before any state
   - Licensing board, federal agency, or court of law concerning the professional conduct of the PI as a research investigator or as a clinician
5. A **Conflict of Interest (COI) Disclosure Form for Investigative Sites** or equivalent client form must be completed if the PI or study team member has a potential COI.

Note on Study-level Approvals and New PI Approval Packets

When investigators are approved for a study, the PI approval packet generally only includes the investigator's IRB approval letter, consent form, and any site-specific materials submitted with the PI's submission. Study-level materials (e.g. recruitment materials, copy of the protocol, IB, Dear Investigator Letters) are not directly sent to the investigator. Study-level IRB approved documents are listed in the PI approval letter and are available for retrieval through Connexus.

B. Change in Principal Investigator (Transfer)

It is the responsibility of the currently approved Principal Investigator and the new investigator to ensure that proper transfer documentation is completed before the new PI begins.

An investigator cannot take over as PI for a study until he or she has been approved by CGIRB. This includes investigators who may have been sub-investigators listed on the Form FDA 1572. Approval by the sponsor does not equate IRB approval so the site must ensure that IRB approval is obtained for the new PI prior to the transfer.

In order for a change in PI to occur, CGIRB requires the following for review:

- All documentation required for an initial PI submission
- Any new/updated recruitment items to be used by the new Principal investigator should be submitted at this time.

- The **Principal Investigator Transfer Form** must be submitted to CGIRB by the investigator who will no longer be the acting PI and must be completed by that individual or his/her designee.

Submitting the PI transfer documents prior to the transfer ensures that IRB approval does not lapse for the site. As most PI transfers are planned in advance, CGIRB expects the transfer documentation to be submitted prior to the transfer. An investigator's failure to obtain IRB approval at transfer may be considered noncompliance.

There are circumstances where a transfer may occur without sufficient time to submit to the IRB (e.g. death of investigator). CGIRB expects to be notified within 3 weeks of an unexpected transfer with submission documents for the new Principal Investigator submitted.

C. Promptly Reportable Information

Consistent with FDA Guidance, we encourage submission *only* of events that meet the definition of a reportable event, and as such, our new form is designed to help sites and sponsors determine which events may require reporting.

Use the CGIRB **Promptly Reportable Information** form to report the following *information to us within 5 days of your knowledge of the event.*

- New or increased risk
- Protocol deviation that harmed a subject or placed subject at risk of harm
- Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a subject
- Audit, inspection, or inquiry by a federal agency
- Written reports of federal agencies (e.g., FDA Form 483)
- Allegation of Noncompliance or Finding of Noncompliance
- Breach of confidentiality
- Unresolved subject complaint
- Suspension or premature termination by the sponsor, investigator, or institution
- Incarceration of a subject in a research study not approved to involve prisoners
- Adverse events or IND safety reports that require a change to the protocol or consent
- State medical board actions
- Unanticipated adverse device effect
- Information where the sponsor requires prompt reporting to the IRB

Information not listed above does not need to be reported to the IRB.

D. Changes at the Research Site

All changes at your research site (e.g., address changes, phone number changes, site-specific consent document wording changes) should be submitted to CGIRB using the **Change in Research** form.

E. Advertisements/Recruitment Materials

All advertisements and other subject recruitment or retention materials must be submitted to CGIRB for review. These items **must be approved** by CGIRB **prior** to their use. Please submit photos only of subject incentive items such as t-shirts, bags, pens; CGIRB does not require the submission of these actual items.

All audio and video materials should be accompanied by the script. To avoid unnecessary additional production costs due to re-work, it is strongly recommended that CGIRB 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 CGIRB for review, CGIRB 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 CGIRB for final approval before use with subjects and MUST match the CGIRB approved script.

Advertisements should include the information prospective subjects need to determine their eligibility and interest in participation in the research. Review of advertisements may include information such as:

- All the information contained in the advertisement
- Mode of its communication
- Final copy of printed advertisement(s)
- Final audio or video taped advertisement(s)
- Name and address of Investigator or research facility
- Location of the research and person or office to contact for further information
- Purpose of the research or condition under study
- Summary of criteria used to determine eligibility
- Brief list of benefits to subjects, if any

- Time or other commitment required of subjects

Advertisements should include the following elements:

- Statement that this is a "research study," "clinical research trial," "clinical trial," or "clinical study" such that the potential subject knows that the advertisement is for research and not clinical care. (Terms are considered synonymous under 21 CFR 56.102(c))
- References to free medical treatment must be qualified with "research-related" or "study-related."
- The words "medicine" or "medication" must be qualified with terms such as "research," "investigational," "experimental," "study," etc. unless the compound under study is approved for the condition described in the advertisement. It should be clear that the drug is not approved.

Advertisements cannot:

- Imply or express claims of safety or effectiveness of study medication or equivalence or superiority to another drug; or make claims, either explicitly or implicitly, about the test article under investigation that are inconsistent with FDA labeling.
- Include undue emphasis on subject compensation (such as the payment amount being bolded, underlined or exaggerated font size). It is acceptable to have the word "free" unless it is related expressly to "medical care" or "treatment." "Free" should NOT be bolded or underlined or emphasized in any way, but actually having the word "free" does not present a problem, when qualified as "study-related". Avoid "free treatment" when the intent is only to say subjects will not be charged for taking part in the investigation.
- Claim that the research "will" (as opposed to "may") improve the subject's medical condition. The ad cannot state or imply a certainty of favorable outcome or other benefit beyond what is outlined in the consent document and the protocol.
- Express or imply that the research is FDA approved. Terms such as "new treatment," "new medication," or "new drug" should not be used without explaining that the test article is investigational or experimental.
- Include the actual drug names or the sponsor name, unless the sponsor approves its use.
- Include exculpatory language, that is, appear to waive the subject's legal rights.
- Include information that is incorrect according to protocol.
- Offer compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

Telephone and Web-based Screening

In analyzing screening scripts, the following elements should be present:

- Voluntary Participation, including the right not to answer a question (or skip) if a subject does not want to answer;

AND

- Confidentiality, including that the information collected will be destroyed if the subjects do NOT give their permission to keep it in a database if they are not eligible.

Examples of Introductions

"In order to determine if you qualify for this research study, I am going to ask you some personal questions about your health and present condition. You may stop answering questions at any time and you do not have to answer any question that makes you uncomfortable."

OR

"Completion of this interview is voluntary. You are free to end this interview at any time."

Examples of Conclusions

"Based on the information that you have given us, it appears you do not qualify for this research study. {With your permission, we will keep this information on file for your possible qualification in a future study.}* Do we have your permission to retain in our files information collected in this (telephone) conversation?" YES NO

If "NO," then "We will destroy this information immediately."

* Not necessary to add this part unless there will be re-contact with that person.

F. Subject Payments

CGIRB reviews payments to determine that such arrangements are fair, accurate and appropriate in the context of the research. Evaluation of payments shall include the following:

- The amount of payment and the proposed method and timing of disbursement is neither coercive nor presents undue influence. Site-specific changes may require a justification and /or sponsor approval.
- Credit for payment accrues as the study progresses and may not be contingent upon the subject completing the entire study.
- Any amount paid as a bonus for completion must be reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.
- All information concerning payment, including the amount and schedule of payments, is set forth in the consent document.

G. Protocol Amendments, Revised Informed Consent Forms, and/or HIPAA Authorization Language

All protocol amendments must be submitted to CGIRB for review and approval prior to implementation. The sponsor does not have the authority to implement any significant change to the protocol without the review and approval of the IRB of record. You must have CGIRB approval **before** you implement the proposed amendment or change. However, a protocol change intended to eliminate an apparent immediate hazard to subjects may be

implemented immediately provided the agency is subsequently notified by protocol amendment and CGIRB is notified in accordance with the applicable regulations.

Administrative changes that do not significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study must be submitted to CGIRB but do not require approval prior to implementation.

Examples of administrative changes are:

1. Corrections of typographical errors
2. Changes to sponsor contacts, such as the medical monitor
3. *NOTE: If an amendment requires changes to the ICF, please track changes on the approved version of the ICF and submit it with the amendment.*

H. Changes to the Clinical Investigator Brochure (CIB)

It is the sponsor's responsibility, as the overall investigation proceeds, to keep each participating PI informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to PIs by the following:

1. Periodically revised CIBs
2. Reprints or published studies
3. Reports or letters to PIs
4. Other appropriate means

Important safety information is required to be relayed to PIs in accordance with 21 CFR 312.32 and this information may need to be submitted to the IRB (see Section III on promptly reportable events). Changes to the ICF may occur based on information received (as above). Revised ICFs may be submitted by the sponsor, CRO, institution, or PI.

In some instances, sponsors or CROs may make arrangements to make submissions of updated CIBs or other safety information (as above) on behalf of the PIs. It is your responsibility to verify submission arrangements to ensure your regulatory responsibilities are met. Again, please note that if updated safety information is reportable under CGIRB's policy on unanticipated problems, the reports must be made to CGIRB promptly, and in all cases within 5 days of the site's awareness of the event.

I. Study Status – Continuing Review

Federal regulations require that, at a minimum, research projects are reviewed no less than annually. The approval period may be shorter for studies that may pose a greater risk or where critical information relevant to risk and benefit may be available on a periodic basis. As the PI for your study, you are responsible for submitting a CGIRB **Site Continuing Review Report** at the appropriate intervals.

CGIRB support staff will notify you in writing approximately two months in advance of the deadline for submission of the continuing review documentation. You may delegate the task of making submissions to CGIRB to a qualified individual; however, as the PI, it is your responsibility to ensure all reporting requirements are met. A PI's failure to complete and

return the requested continuing review information to CGIRB by the end approval date results in the loss of IRB approval.

If subjects are enrolled at the site and CGIRB approval expires, the investigator is required to submit a transition plan for all active subjects to CGIRB in writing within five business days.

Failure to submit complete continuing review information by the study expiration date does not qualify for an appeal. PIs who do not receive CGIRB re-approval because of failure to submit the requested information are considered to be noncompliant with CGIRB reporting requirements. Additionally, these investigators may be reported to the Sponsor/CRO and the appropriate federal regulatory agency (e.g. FDA, OHRP).

J. Study Status - Closure Report

A **Principal Investigator Closure Report** should be provided for your site when the close out visit occurs, or in the absence of monitoring, when the study summary is provided to the sponsor. The **Principal Investigator Closure Report** must be submitted to CGIRB within 90 days of site closure. In turn, CGIRB will send a letter of acknowledgement regarding the closeout notification.

If you expect subjects to remain in the study for any reason, you may not close your site.

IV. ADDITIONAL USEFUL INFORMATION FOR INVESTIGATORS

A. HIPAA Authorization

"HIPAA" stands for the Health Insurance Portability and Accountability Act. The Privacy Rule within this regulation outlines the standards for privacy for individuals and confidentiality of individually identifiable health information. The specific regulations for HIPAA are in Title 45 CFR 160 and 164.

As a clinical investigator, you need to assess if you are a covered entity as defined by the Office of Civil Rights. All PIs who are covered entities must have HIPAA Authorization language for potential subjects in order for study-related medical records to be available for review by the sponsor, CRO, IRB, and regulatory bodies. For your studies under the approval of CGIRB, your HIPAA authorization language must be submitted to CGIRB and be CGIRB-approved prior to its use.

CGIRB may approve a request for waiver/alteration of authorization provided that the CGIRB Board or Expedited Reviewer determines that the alteration or waiver of authorization satisfies the regulatory criteria outlined in 45 CFR 164. See CGIRB's **Request for Waiver/Alteration of HIPAA Authorization Form**.

B. State and Local Laws

As PI, it is your responsibility to be aware of and comply with any state and/or local laws that raise the standard of research conduct or affect The Privacy Rule as currently outlined in the federal regulations. Any additional elements relevant to the state/local requirements must be submitted to CGIRB for inclusion in your site-specific ICF. If you are unsure about the

state or local laws you should contact your study sponsor or a health care attorney in your area.

C. Safety Monitoring

Safety monitoring should take place throughout the study. As the PI it is your responsibility to provide CGIRB with any safety information that might impact subject rights and welfare. CGIRB should be sent copies of any interim analyses and/or DSMB summary reports as they are made available to the PI.

D. Investigator Noncompliance

CGIRB expects PIs to conduct CGIRB-approved research activities in accordance with CGIRB's requirements, as set forth in this Guidebook and in compliance with all federal, state, and local regulations. CGIRB defines investigator noncompliance as the failure to follow the applicable regulations and/or the requirements and determinations of CGIRB.

Examples of Noncompliance

The following are examples of investigator noncompliance. This list is not meant to be all-inclusive. Please reference the **Promptly Reportable Information** form. The actions of anyone in the Human Research Protection Program may result in noncompliance if one of the following occurs:

- Performing human subject research without first obtaining IRB approval or an IRB declaration of exemption.
- Deviating from or violating the provisions of an IRB-approved protocol when the deviation harms a subjects or placed subjects at risk of harm.
- Failing to secure IRB approval of a protocol due for periodic continuing review prior to its expiration date.
- Permitting a protocol's IRB approval to lapse without stopping all research-related activities and submitting a Principal Investigator Closure Report to the IRB or, in the event of an overriding safety concern or ethical issue such that it would be in the individual subject's best interest to continue study participation, arranging with the IRB to continue those activities.
- Failure to report complaints or results of audits to the IRB.
- Failure to follow the regulations or the requirements and determinations of the IRB.

If evidence is received by CGIRB to indicate potential noncompliance, the CGIRB Board reviews this information and determines appropriate actions, including, but not limited to:

- Temporary suspension or termination of all or some previously approved research activities (suspensions and terminations of previously approved research are reported to applicable regulatory authorities in accordance with federal regulations).

- Determination of serious or continuing noncompliance (in accordance with federal regulations, serious and/or continuing noncompliance is reported by CGIRB to the applicable regulatory authorities).
- Request for the conduct of an investigator site visit.
- Communication with the PI to document the issues and to provide the opportunity to respond.
- Request for additional information from the PI, submitting body, or other source.
- Other actions as determined by the CGIRB Board.

CGIRB reserves the right to visit your site and/or interview your sponsor or others as needed to assess possible noncompliance issues.

E. Suspensions and Terminations

Federal regulations require that an IRB have the authority to suspend or terminate approval of research or investigators. Copernicus Group IRB may suspend or terminate CGIRB approval of previously approved research or investigators under the following circumstances:

a. When research is not conducted in compliance with federal, state, and local requirements and in accordance with CGIRB requirements, or

b. When the risk-to-benefit ratio no longer justifies continuing the study (based on information received by CGIRB related to safety or other unanticipated risks to research subjects or others).

When suspensions or terminations occur, the PI is required to send the Board a written course of action that will be undertaken to ensure the protection of the rights and welfare of each enrolled research subject. Additionally, if the suspension or termination is for investigator noncompliance, CGIRB reserves the right to initiate immediate review of all the PI's active studies at CGIRB.

The CGIRB Board Chairperson reserves the right to suspend or terminate activity for all other CGIRB-approved studies until a convened Board has made a determination. If CGIRB terminates or suspends approval of the clinical trial, the Investigator must promptly notify the Sponsor.

In accordance with federal requirements, suspensions or terminations of previously approved research or investigators are reported by CGIRB to the sponsor and to the appropriate regulatory authorities.

F. Appeals Process

When a research study or investigator is disapproved, or the CGIRB Board suspends or terminates previously approved research or investigators, the submitting body has a right to appeal the CGIRB Board's decision. If a submitting body decides to appeal a CGIRB Board decision, the appeal may be made in writing or at a routinely scheduled Board meeting, via teleconference or in person. Arrangements for participation in a convened Board meeting must be made in advance through the study-specific CGIRB point of contact or a member of IRB Services.

For disapproved research submissions or disapproved PIs, appeals must be made by the submitting body within 30 business days of the CGIRB Board's decision.

For suspensions and terminations of previously approved research activities, appeals must be made by the submitting body within 10 business days of the CGIRB Board's decision.

If an appeal is made, the CGIRB Board reviews the resubmitted information at a convened IRB meeting. If disapproved, the written notification of disapproval is provided and clearly states the reasons for the CGIRB Board's decision. Once the decision is made to uphold the initial disapproval, the submitting body must abide by the decision made by the CGIRB Board.

V. REFERENCES

HELPFUL WEBSITES

For additional information see the CGIRB website or the following links:

- http://www.cgirb.com/investigators/ (Investigator-related information on CGIRB's Website)
- http://www.fda.gov/oc/ohrt/irbs/default.htm (FDA Information Sheets)
- http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ComplianceEnforcement/default.htm (FDA Compliance & Enforcement)
- https://www.cms.gov/Regulations-and-Guidance/Administrative-Simplification/HIPAA-ACA/AreYouaCoveredEntity.html (Covered Entity Decision Making Tool for the Privacy Rule)