1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

WCG IRB Guide for Researchers

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Contents

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Introduction

WCG IRB is pleased to provide this handbook of information about using us 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. Please use the information in any way that will serve to assist your research efforts as we join together in protection of human research participants.

Working with WCG IRB for IRB Review - An Overview

New protocols submitted to WCG IRB for review (that are not eligible for expedited review) are assigned for review based on the next available panel meeting. US panels meet daily. Reviews for investigators at Canadian locations are assigned to the Canadian panel; therefore, a protocol taking place in both the United States and Canada will be assigned to both U.S. and Canadian panels.

WCG IRB conducts expedited review of certain kinds of research involving no more than minimal risk to human research participants according to the federal regulations. 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.

To learn more about accessing research review details, WCG IRB's panel structure, or to determine the panel assignment of a protocol, call client services at 855-818-2289 or email clientservices@wcgirb.com

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

Confidential Disclosure Agreements (CDAs) between sponsors and WCG IRB are not required by WCG IRB. However, we are happy to enter into a CDA if preferred by the sponsor. If you require a CDA, your request will be directed to WCG's General Counsel for preparation. WCG IRB requires an indemnification agreement signed by sponsors for protocol submissions.

Submitting Documents for IRB Review

Set up an account or log in to WCG IRB Connexus to submit a new study.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Clients of WCG IRBNet or WCG Velos may submit new studies through their respective portals.

Materials required for Initial Review

Following is a general list of items required by WCG IRB to begin the review process for a research study.

Items Required for All Initial Review Requests

Initial Review Submission Form For best results, WCG IRB recommends use of WCG IRB Connexus for study submissions.

Protocol

Current Professional License for principal investigator (PI), showing the expiration date

(Federal regulations do not recognize coprincipal 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 WCG IRB has not already approved one). Please submit consent forms as Microsoft Word compatible files (.doc, .docx, .rtf).

Other Materials to be Provided to the Participants which are not included in the protocol, such as advertisements, questionnaires, participant 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.)

For drugs, biologics and food supplements

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, please submit the 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.wcgirb.com.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

For device studies:

Device manual is required for device studies (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) for treatment, not part of a research study, may use the form titled Clinical Use of a Humanitarian Use Device (HUD) (HRP284)_ designed for such review requests.

Regulations Affecting Clinical Research, Including HIPAA: The Regulatory Framework Within Which WCG IRB functions

IRB Compliance Statement

WCG IRB is duly constituted and has written procedures in compliance with requirements defined in 21 CFR Parts 50 and 56, 312, 812, 45 CFR 46 and ICH Guidelines relating to Good Clinical Practice. WCG IRB's mission is to ensure that research is conducted ethically according to the principles of the Belmont Report and in compliance with all federal and international (ICH) regulations, state laws and that the rights and welfare of human participants are protected.

WCG IRB is registered with FDA/OHRP.

WCG IRB registration number is IRB00000533, and WIRB's parent organization number is IORG0000432.

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

- 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 participants. 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 WCG IRB client services at 1-800-562-4789 or 1-617-243-3924 or clientservices@wcgirb.com.

WCG IRB can help researchers and institutions comply with the NIH Single IRB policy – go to our institutions page for more information.

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.

WCG IRB has established written procedures that ensure that research approved by WCG IRB meets these three primary standards. However, WCG IRB 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 participant 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 participant.

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

HIPAA

WCG IRB also provides services under the Privacy Rule (45 CFR Parts 160 and 164 of the Health Insurance Portability and Accountability Act of 1996). WCG IRB will review requests for waivers of authorization and partial waivers of authorization for covered entities upon request (WCG IRB forms for requesting review of partial and full waivers of authorization are available on the on the Forms page of www.wcgirb.com). WCG IRB 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. WCG IRB will review separate authorization documents upon request.

Conflicts of Interest

To meet the needs of its clients and 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," WCG IRB 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 Forms page of www.wcgirb.com.

WCG IRB 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.

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;

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

- 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;
- Any governance or executive relationship with the sponsor (e.g., board of director, CEO)
- 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 participants; or
- Is affiliated with an institution that has 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 Aug. 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] (https://grants.nih.gov/grants/policy/coi/index.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).]

WCG IRB also requires investigators and their research team to report planned recruitment bonuses. WCG IRB defines a recruitment bonus as an additional payment or incentive provided to the investigator or staff dependent solely on a number of participants being enrolled, or dependent on the speed at which participants are enrolled. The term "payment or incentive" includes any items of value, such as direct payment, gift certificates, travel vouchers, physical items such as watches, and so forth. Report such incentives in the initial review smart form available on www.wcgirb.com.

A financial conflict of interest is not intrinsically wrong. Rather, the purpose of analyzing a financial conflict of interest is to determine when the interest offers incentive to the investigators or other party to breach a duty to participants or to society, and to determine how to address the conflict of interest. As individuals vary in their personal integrity, and as the WCG IRB board generally does not know investigators and other parties intimately enough to judge their integrity, WCG IRB 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.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 participants 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 participants. In a study involving the analysis of human tissue, the risks to the participants 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 participants to enroll, clinical care provided to the participants, use of participants' 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 Participants

Many of the concerns about the conflicted party's decisions will be lessened if the conflicted party does not interact directly with participants. For example, in many tissue studies the conflicted investigator simply receives waste samples from a surgery facility, and has no contact with the participants. 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 inquiries about conflicts of interest at certain procedural steps.
- Some institutions have assigned participant advocates who sit in on the consent process.

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 Qualifications:

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 participant safety or bias the investigator's decision-making and does not require further action.
- A finding that disclosure of the conflict to participants 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.

Compensation to Investigators for the Conduct of Research

Financial compensation to investigators should be at fair market value for the procedures and services provided. WCG IRB 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 Opinion 11.3.4).

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

The Informed Consent Process

The informed consent process is central to the ethical conduct of research. It is an ongoing conversation between the human research participant and the researchers that begins before consent is given and continues until the end of the participant'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.

Goals for the informed consent process

Give the participant information about the research

Make sure the participant has time to consider all options

Answer all the participant's questions before the decision is made

Make sure that all information is understood by the participant

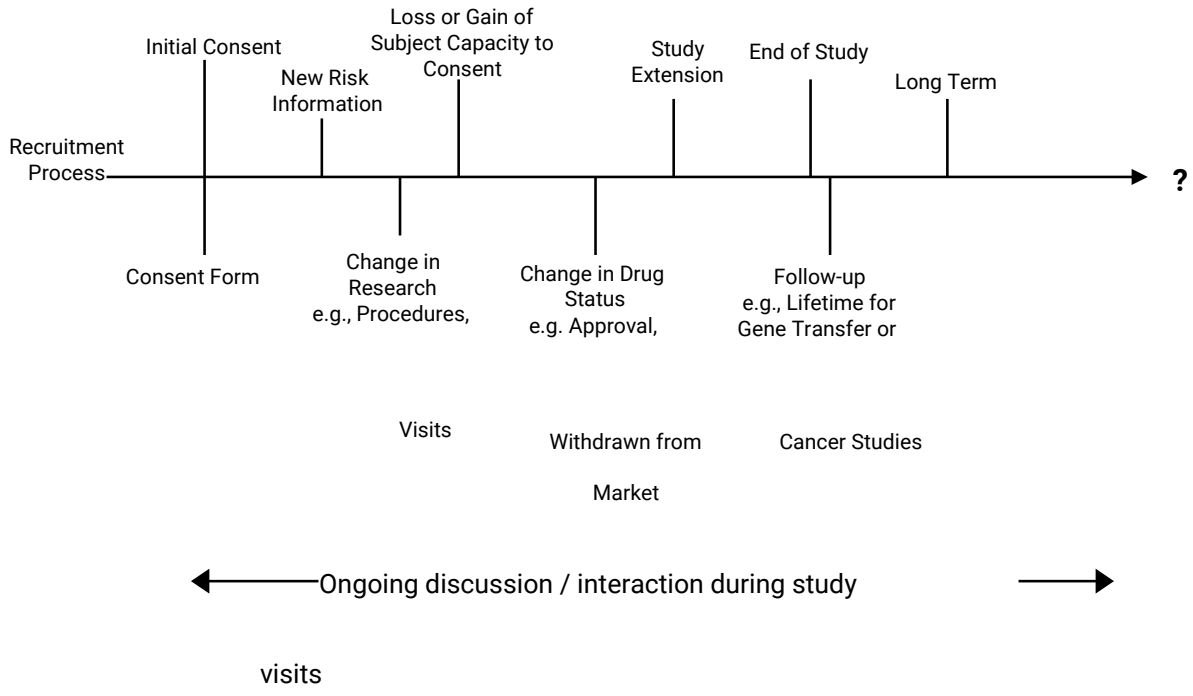
Obtain the participant's voluntary informed consent to participate

Continue to inform the participant throughout the research study

Continue to re-affirm participant consent to participate throughout the research study

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Consent process diagram



Issues to consider during the consent process

- Was the participant alert and, in your opinion, able to read and understand the language in the consent form?
- If the participant 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 participant, who reads the informed consent form and any other written information supplied to the participant, and who is willing to attest to this by signing the consent form.)
- If the participant is not fluent in English, was an approved translation of the consent form provided in the primary language of the participant? Was there also a bilingual translator present to assist with the informed consent process? Note: a translator alone is not considered adequate.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

- Was the participant under any pressure (for example, family pressure, lack of medical insurance) to participate in the research? Was this discussed?
- Did the participant 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 participant?
- Are there any other risks or concerns not stated in the consent form and were these explained to the participant?
- Was the participant asked if he or she had any questions about the study?
- Did the participant have any questions or concerns?
- Were the participant's questions answered?
- Was the participant satisfied with the answer(s) they were provided?
- Did the person conducting the consent discussion check for participant understanding by asking some basic questions about the research? Did the responses reflect adequate understanding?
- Did the participant 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 participant, were additional concerns about the participant's understanding and assent considered and addressed?

Investigator responsibilities regarding informed consent

- Obtain consent before initiating study-specific procedures.
- Give the person providing informed consent as much time as they need to make a decision.
- Provide a quiet, comfortable, and private setting for the informed consent process whenever possible.
- Explain the consent process to the participant.
- Make sure the participant has time to consider all options; allow participant to take the form home before signing (whenever possible). If the person providing informed consent needs more time than is allowed by the research design, not enroll the prospective participant.
- Evaluate whether the person providing informed consent is experiencing time pressure to make a decision, and if so, do not enroll the prospective participant, even if the person providing informed consent agrees to be in the research.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

- Ensure there is no threat of harm or adverse consequences to the prospective participant for a decision to not take part in the research.
- Stop the informed consent process once the person providing consent indicates that he or she does not want to take part in the research.
- Evaluate whether the person providing informed consent is being coerced or unduly influenced by others to take part in the research, and if so, not enroll the prospective participant, even if the person providing informed consent agrees to be in the research.
- Communicate in the preferred language of the person providing informed consent.
- Adapt the presentation of the information to the participant's capacities in terms of intelligence, rationality, maturity and language.
- Invite and answer questions from the person providing informed consent.
- Evaluate whether the person providing informed consent understands the information provided, and not enroll a prospective participant who does not understand, even if that person providing informed consent agrees to be in the research.
- Ensure that no information is provided to the prospective participant or the person providing informed consent that is made to waive or appear to waive any of the prospective participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.
- Communicate to the person providing informed consent all the information in the consent document or script approved by the IRB.
- Invite and answer questions from the person providing informed consent.
- Not enroll a prospective participant when the person obtaining informed consent is unwilling to listen to or consider the information, even if the person providing informed consent agrees to be in the research.
- Consider the participant's reading abilities. Check to make sure the protocol does not exclude participants 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 participant understands enough information about the research study to give informed consent.
- To the extent possible, make sure the participant can consent free from coercion or other undue influence.
- Since the informed consent process continues throughout participation in the study, consent should be informally verified on a continuing basis.
- Significant new information must be given to the participant, and continuing consent documented in some way; for example, new risk information presented to the participant in an addendum to be signed by participants who agree to continue to participate.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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.*

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). These regulations define LAR as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participation in the procedure(s) involved in the research. We recommend you consult your state law and if necessary, obtain legal counsel to determine who represents a LAR for your research.

Trials involving adults who lack the capacity to personally provide informed consent, unless an exception is justified, should be conducted in individuals having a disease or condition for which the investigational product is intended.

WCG IRB'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 LAR under their state/provincial and local law. WCG IRB can provide a copy of the relevant statutes for your state upon request; however, advice from your legal counsel is strongly recommended. 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 participant to participate in the procedures involved in this research protocol are _____." Sites should also be able to explain the process they use for verifying that an individual is qualified to serve as a LAR.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Consent by Participants Who Cannot Physically Sign the Consent Form

WCG IRB does not require a Legally Authorized Representative to provide consent for participants who are *cognitively capable* of consenting, but *physically* unable (for example, due to paralysis). In those cases, obtain consent from the participant with the assistance of a witness (see Witness section below).

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 participants.
2. The research could not practicably be carried out without the waiver or alteration
3. If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the participants.
5. Whenever appropriate, the participants will be provided with additional pertinent information after participation.

WCG IRB applies this standard to all requests for waiver of consent for non-FDA regulated research

Waivers of Consent for FDA studies

In July 2017, the FDA issued new guidance titled "IRB Waiver or Altercation of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects"; the guidance states "FDA does not intend to object to an IRB waiving or altering informed consent requirements for certain minimal risk clinical investigations as described in Section IV of this guidance." Prior to that guidance, 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. Because the 2017 guidance covers all the situations covered in 2006 guidance and easier to implement, the IRB will use the 2017 guidance in lieu of the 2006 guidance.

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).

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 Board will need to review the information that is provided to participants to obtain consent to ensure that the required elements of consent are included in the consent discussion. If you are requesting a waiver of documentation of consent, please submit a written statement or script of this information for the Board's review, a "participant information sheet." To create one, use the template consent, change the title to "PARTICIPANT INFORMATION SHEET" and delete the signature blocks.

The regulations that allow the board to approve this type of waiver:

For FDA or HHS regulated research (21 CFR §56.109(c)(1) and 45 CFR §46.117(c)(1)(ii)):

The research presents no more than minimal risk; and

The research involves no procedures for which written consent is normally required outside of research context

For HHS regulated research (not applicable under FDA regulations) (45 CFR §6.117(c)(1)(i)):

The only record linking the participant and the research would be the consent document and the principal risk of the research is the risk of breach of confidentiality.

Each participant will be asked whether the participant wants documentation linking the participant with the research, and the participant's wishes will govern; and

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

For HHS regulated research (not applicable under FDA regulations) (45 CFR §6.117(c)(1)(iii)

If the participants or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to participants and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

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.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Clinical investigators need to assess if they are a covered entity as defined by the Office for Civil Rights. All PIs who are covered entities must have HIPAA Authorization language for potential participants 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 WCG IRB, your HIPAA authorization language must be submitted to and be approved prior to its use.

WCG IRB will review research materials to determine how the privacy and confidentiality of participants' personal health information is protected in accordance with applicable laws and regulations. The burden of HIPAA compliance rests with the covered entity.

Researchers who are covered entities and do not wish to request a waiver, may satisfy the HIPAA requirement for authorization by choosing one of the following alternative methods:

- Obtain a HIPAA compliant signed authorization from the research participant using a stand-alone document that the covered entity has created; or
- Incorporate the HIPAA language into the ICF and submit to WCG Aspire IRB for review in accordance with applicable laws; or
- Attach an addendum that contains the HIPAA language to the ICF and submit to WCG Aspire IRB for review in accordance with applicable laws.

WCG IRB will 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. WCG IRB will review separate authorization documents upon request.

Waiver of Authorization for Use and Disclosure of Protected Health Information

If you are a covered entity or your organization must otherwise comply with the HIPAA, and the research requires you to use or share identifiable health information, you must obtain an authorization for the use and disclosure of protected health information. If this is not practical, you need to request a waiver of authorization. If you are requesting a waiver of consent or written documentation of consent, you also need to request a waiver of authorization. The necessary information is collected via our Initial Review Smart Form, or can be provided via the stand-alone form "Requestfor Full Waiver of Authorization Under HIPAA" available on the forms of www.wcgirb.com

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Assent

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

Assent is usually required for research involving *underage participants* and research involving *adults with diminished capacity*. Assessing an adult's capacity to consent may be somewhat difficult, depending on the participant's medical/mental condition and the requirements of the protocol. If the investigator anticipates that some participants 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 participant is best protected by involving a LAR who knows the participant and is willing and able to participate in the informed consent process with the potential participant.

In order to assent, a participant must have at least a basic understanding of what might be asked of them in the research and what might happen to a level consistent with the participant's capacity to understand.

The additional challenges an investigator faces in the assent process depend on the level of understanding the participant may be able to achieve. This will vary with each individual potential participant. An investigator may be able to obtain information about the participant'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 participant and researcher. At times this may mean having a different individual conduct the assent process to optimize the communication.

WCG IRB 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 participant. Some state and local laws also further restrict enrollment of wards in research.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 document must be accurate and complete
- 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.
- The investigator must give the participant or LAR adequate opportunity to read it before it is signed and dated
- The document must be signed and dated by the participant or LAR
- The document must be signed and dated by the person obtaining consent
- For clinical research: If the participant cannot read, an Impartial Witness must witness the consent process and sign and date the form
- A signed and dated copy must be given to the person signing the form

Assent Forms

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

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

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. FDA has issued guidance titled Use of Electronic Informed Consent.

Electronic consent can describe the exact representation of the IRB-approved document on an electronic device to a consent process using electronic devices and audio-visual aids.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

WCG reviews the electronic (e-consent) platform onto which the study and site IRB approved consent forms are uploaded as a participant material template at the study level. Each site that intends to utilize the platform is not required to submit the platform with their site-specific consent form, instead, they will be reviewed for the study level version only, with the expectation that their site-level consent form will be uploaded.

Simple representation of an IRB approved document on an electronic device requires the signatures be confirmed to be 21 CFR part 11 compliant and a certificate of authenticity.

Other electronic consent processes that are not just simple electronic representations require further details to be submitted. WCG IRB 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

Preferred Vendor for e-Consent

In 2017, WCG acquired Patient Genesis' ConsentNow™ eConsent technology. ConsentNow improves the informed consent process by enabling healthcare companies to share important information with patients in a clear, easy-to-understand electronic format.

The technology employs custom video and animation segments to educate patients and online knowledge assessment questions to determine their level of understanding. This multimedia experience is delivered directly to the patient using a tablet device at the clinical site.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Knowledge empowers patients to make the best decisions for themselves and for their families - using a patient-friendly format that includes plain language, videos and animation, ConsentNow helps to ensure that patients truly understand the benefits and risks of their clinical trial participation.

In global clinical trials, communication can often pose significant challenges; ConsentNow enables providers to deliver important information in the patient's native language and capture their feedback via questionnaire. This helps to eliminate confusion for the patient and increase efficiency for the trial's sponsor.

In addition to improving the quality of patient education and the consistency of trial communications, ConsentNow fosters regulatory compliance because it is always loaded with the latest version of the protocol and will not allow the consent process to be completed until all required signatures are in place. Another benefit of the ConsentNow solution is increased patient retention, as patients who are better informed at the start of the trial are less likely to drop out. And with a secure, web-based dashBoard, it provides both the sponsor and clinical site team members with real-time access to valuable site statistics.

For clinical trial sites, the ConsentNow technology delivers an easier patient enrollment process, better informed patients, a significant reduction in paperwork, and real-time tracking of patient progress.

Certificates of Confidentiality (CoC)

A CoC 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.

Research studies that are funded by NIH are automatically issued a certificate under the NIH Policy on Certificates of Confidentiality. Non-NIH funded research that collects identifiable, sensitive information can request a certificate from NIH for health-related studies that are not funded by NIH, but the granting of a CoC in these cases will be at the discretion of the NIH.

Investigators might consider applying for a certificate for research involving participant 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 participants involved in illegal, stigmatized, or embarrassing behavior; participants with illegal status (alien, child runaway, AWOL, etc.); and participants with a stigmatized disease

(HIV, alcoholism, mental illness, etc.) might have additional protection if a CoC has been obtained.

If the study for which the CoC is granted involves informed consent, the investigator must inform research participants of the protections and limits on protection provided by the CoC. If language is not included in the consent form, WIRB will insert the following language (or similar):

"Information about a Certificate of Confidentiality for this research:

[Name of research site and investigator] has received a Certificate of Confidentiality from the government which will help protect the privacy of research participants. The certificate protects against the involuntary release of information about participants collected during the course of this research. The researchers involved in this study cannot be forced to disclose any information collected in this study in any legal proceedings.

However, the participant may choose to voluntarily disclose the protected information and this certificate does not prohibit such voluntary disclosure. Furthermore, the parties listed in the Confidentiality / Authorization section of this consent form may review our records under limited circumstances and this certificate does not prohibit such disclosure."

For some types of research, the Board may direct an investigator to obtain a certificate of confidentiality.

Frequently asked questions about CoCs are available on the NIH web site here: https://humansubjects.nih.gov/coc/faqs and OHRP has posted guidance here: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/certificates-ofconfidentiality/index.html. Instructions for applying for a Certificate are available here https://grants.nih.gov/grants/policy/coc/appl_intramural.htm . 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 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: https://www.nij.gov/funding/humansubjects/pages/confidentiality.aspx .

WCG IRB Policy on Pregnant Partners

Effective Jan. 22, 2018, WCG policy on collection of outcome data on partners of study participants has changed. WCG policy is now as follows: the collection of outcome data on

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

partners of study participants who become pregnant does not meet the HHS definition of research, because it does not represent a systematic investigation designed to develop or contribute to generalizable knowledge. As a result, the IRB will no longer be making 45 CFR 46 Subpart B or D determinations for follow up of pregnant partners and their children.

If the protocol states that this procedure will occur, consent documents should continue to inform participants of the plan to collect data if their partner becomes pregnant.

If you submit a consent document for pregnant partners, the IRB will review the document as a research consent form. However, if you do not submit a consent document for pregnant partners, the IRB will not require one.

This change does not affect the follow-up of participants who become pregnant. Those individuals are human participants. Such data collection needs to be described in the consent document. Subpart B determinations are required to collect data about the pregnancy. Subpart D determinations are required to collect data about children resulting from the pregnancy.

Requirements for Human Research Protection Training

WCG IRB 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 protection. Your institution may have additional training requirements, please check with your institutional official. Please note that HIPAA training or prior research experience alone does not satisfy this requirement for training in human research protection. Physicians and their teams who request approval of approval of Clinical Use of a Humanitarian Use Device (HUD) or compassionate use of a drug, biologic, or device are not required to complete training on the ethics and regulations of human research protections.

WCG IRB's expectation is that training include topics such as ethical principles related to human research protections, federal regulations for protection of research participants, 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, WCG IRB only requires human research 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.

WCG IRB 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 WCG IRB.

Online:

- WCG IRB is a participating organization in the Collaborative Institutional Training Initiative (CITI). Investigators can meet the training requirement through CITI or CITI International. CITI training for U.S. research is available at: https://www.citiprogram.org. CITI International training for non-U.S. or international research is available at: www.citiprogram.org. (The international course is available in English, Spanish, and Chinese. Additional languages may be available in the future.)
- ACRP Certified Principal Investigator Training (CPI certification)
- DIA Clinical Research Certificate Program
- OCRA Clinical Research Professional (CRP)
- Canadian researchers are required to complete training through the Tri-Council Policy Statement (TCPS) before their submission will be approved. The TCPS 2 Tutorial Course on Research Ethics (CORE) is available online in English http://www.pre.ethics.gc.ca/eng/education/tutorial-didacticiel and French http://www.ger.ethique.gc.ca/fra/education/tutorial-didacticiel.
- The NIH Office of Extramural Research provides an online tutorial called "Protecting Human Research Participants" http://phrp.nihtraining.com/users/login.php.

Special Considerations for Drug Research: Do you need an IND

WCG IRB's Initial Review Submission Form asks for information about an IND. As a general rule, WCG IRB 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:

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 WCG IRB 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 WCG IRB.

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

Special Considerations for Device Research: IDE, NSR (Nonsignificant risk) and IDE Exempt

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.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 WCG IRB.

The submission form will prompt you to provide the appropriate, required documentation for review of research involving an SR device. The Board will automatically consider research with an IDE to be SR. In most cases, submitters should ensure WIRB receives a copy of the IDE letter that has not been redacted. Redacted IDE letters generally do not provide sufficient information for the Board. If the research is SR, The IRB requires proof of the IDE number at the time of submission. The Board will automatically consider the research to be SR.

If the participant must undergo a medical procedure as a part of the study, and that medical procedure is not one which the participant would otherwise undergo as part of their care regardless of the research, the Board must consider the risks associated with the procedure as well as the use of the device. If potential harm to participants 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.

Special Considerations for Behavioral Research

WCG IRB reviews behavioral research. Behavioral research is non-clinical research and is oftentimes 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 participant resulting from the deception, and the process for post-study disclosure of the deception and debriefing of the participants, including provisions for psychological counseling or other follow-up which may be needed.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Special Considerations for Federally Funded Research

FWAs

The submission form will prompt you to provide the appropriate, required documentation for review of research involving an FWA. 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:

- 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 WCG IRB is IRB00000533 (Canadian sites use IRB00002354). WCG IRB will request a copy of the DHHS-approved FWA application, but if it is not available, it is not required for review.
- An IRB Authorization Agreement must be completed. The form (Reliance Agreement) is available on the Forms page.

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 WCG IRB's Client Services for clarification or assistance regarding these requirements.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Special Considerations for multi-center studies

Each individual submission for a multi-center study must be accompanied by a completed initial review submission (through the WCG IRB Connexus portal).

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 WCG IRB for information about submission requirements for specific types of research.

Contacts listed in the initial review submission form with the "Copy this person on IRB correspondence box marked will receive copies of the reviewed documents sent to investigators.

Consent forms for multi-center research

Once the board has reviewed and approved a consent form for a multi-center protocol, the IRB 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**. By using the consent form template, you can be confident that you are starting with the most recent IRB and sponsor-approved language, thereby ensuring accurate version control, while saving you time and effort. WCG IRB will generate a consent form for the PI by incorporating any institutionally required language that has been provided to the IRB and the site-specific information such as payment information, etc. into the previously approved consent form template.

Site-specific information which must be provided on the WCG IRB 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 research payment plan are a major source of corrections and research complaints. Also, please be sure your payment plans agree with the sponsor's preferences, if any.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

To determine if a previously approved consent form is available for a particular protocol or request to preview it, contact Client Services at 1-855-818-2289 or check the WCG IRB Connexus page for that protocol (your sponsor or CRO contact can grant you access). If you require customized language, track (redline) your changes on the approved informed consent so we can easily identify your site-specific customizations. Please manually track your changes and do not use Word's "compare" feature to create your redlined consent form, as this may result in more holds and a longer processing time (the compare feature often introduces extraneous formatting changes, duplicative changes, or other changes that are not meaningful, and potentially reverses Board-directed changes).

We require the use of IRB-approved informed consent(s) for initial review submissions of new principal investigators (PIs).

Suggested Guidelines for Evaluating Staff Levels at the Site

Our **initial review submission** asks for information about staffing levels at the site. WCG IRB 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 participant safety or data integrity.
- Enough trained investigators and staff to ensure there is sufficient time available for staff to interact with the participants 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 participants are already enrolled and what is the predicted rate of accrual?
- How many visits are required by the protocol?
- What types of visits are required, and will the participant 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 participants 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 participants considered vulnerable?

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 participants. 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 participants, 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 participant's care and execute the study plan.

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

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 participant recruitment materials or other participant materials (diaries, questionnaires, etc.) that have been previously reviewed by WCG IRB, state in the submission that the items have been previously reviewed by WCG IRB. Board support staff will provide the Board with information about the previous Board review, so that the previous decision of the Board can be considered when the additional materials are reviewed.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Special Considerations for Participants who do not speak English: Translations

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

If you are enrolling non-English speaking participants, you must have plans for conducting the consent discussion in the language understandable to the participant, and for ongoing communication with the participant 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.

WCG-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 participant later qualifies for enrollment, the site can obtain a translated version of the consent form for use in consenting the participant by submitting a request to WCG IRB. The request should identify the sponsor, sponsor protocol number, investigator, and the language requested. The participant cannot be enrolled until they have received the WCG IRB-approved translated consent. If WCG IRB is asked to provide a price quote for the translation, the translation process will not begin until WCG IRB receives authorization to proceed.

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

We suggest 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 WCG IRB translation.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Sponsor/CRO/Site Translations

The WCG IRB-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 WCG IRB 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 WCG IRB staff and an approved copy sent to the site.

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

Submission requirements:

- The translated document (for quicker processing, submit in Microsoft Word format)
- Certificate of Translation, which whenever possible should include:
    1. Document title as it appears on the IRB Certificate of Action
    2. IRB Tracking #
    3. Sponsor Protocol # (if existing)
    4. Study Title
    5. Sponsor name
    6. CRO name (if applicable)
    7. PI name (if applicable, for site-specific translations)
    8. Source and target languages

Sites are required to have Certificates of Translation for each ICF that is translated. We do not require Back Translations for approval of translated documents.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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

_____

(Signature of Translator)

Name of Certification (*ATA, DSHS, other*)_____

Certificate No._____

Unexpected translations: Short form consent documentation process

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

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

The short form will follow the WCG template short form, and the participant will have to be reconsented with the current IRB-approved consent form in a language understandable to the participant within 60 (business) days or at the first visit after receipt of the translated consent form (whichever is less). Some certified short form translations are posted and available for use on the www.wcgirb.com Download IRB Forms page.

Each of the following steps must be followed:

1. The Principal Investigator is to insert study specific information, including title of study, principal investigator, appropriate signature lines (copy from the approved English version or keep the appropriate template ones provided in the translated short forms posted on www.wcgirb.com), and contact information into the OHRP template short form.
2. The participant must be given a copy of the short form in the language understandable to him/her to read;
3. A translator/interpreter must orally present the entire IRB-approved English ICF;
4. The consent process must be witnessed by an individual who is fluent in both English and the participant's language;
5. To utilize the short form consent process, the following signatures are required:

	Required to Sign
Person obtaining consent	Long Form (English ICF)
Witness	Short Form and Long Form
Participant *If the participant is incapable of consent and either a legally authorized representative (as allowed by protocol) or parent(s) signature is required, replace the participant signature block below with the signature block from the IRB approved main ICF*	Short Form

6. The participant must be given signed copies of the English ICF and short form;

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

7. The original signed English ICF and the original signed short form should be retained in the participant's research record and medical record, if appropriate; AND
8. The PI will then obtain a fully translated version of the currently approved consent form at the earliest opportunity. The participant would then be re- consented using the translated consent form within 60 (business) days or at the first visit after receipt of the translated consent form (whichever is less).

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 participant. Some state and local laws also further restrict enrollment of wards in research.

Special Considerations for Unregulated Research in Maryland, New York, and Virginia

Due to the special state laws in New York, Virginia and Maryland in regard to research, WCG IRB has opted to apply the Revised Common Rule as an equivalent regulation to all unregulated (not federally funded or subject to FDA regulation) research in those states approved after January 21, 2019.

As a result, WIRB will require that the consent form has a concise summary and includes the required and appropriate additional elements of consent required under the Revised Common Rule.

Special Considerations for Canadian Research

The WCG Canadian Panel is located in Vancouver, Canada. Its membership is compliant with the requirements outlined in the Division 5 regulations of Health Canada. The Panel is able to review research for Canadian sites that do not need to use their own local research ethics Board. For more information about the Canadian Panel, please call Client Services at 855-818-2289 or the Canadian office in Vancouver at 604-872-5030.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Submitting the No Objection Letter from Health Canada: The sponsor must submit clinical trials of drugs and devices to Health Canada before the study can begin. If there are no objections or issues, Health Canada will issue a No Objection Letter (NOL), typically within 30 days. Review by Health Canada and the Research Ethics Board (REB) may occur in parallel so the NOL may not have been issued prior to Board review. If the sponsor has received the NOL prior to submitting to the REB, they should include it as part of the submission. If the sponsor has not received the NOL prior to submitting to the REB, they should submit it as soon as they receive it.

While the Tri Counsel Policy Statement (TCPS) does not generally apply to the research reviewed by WCG IRB, the Board will apply it to all Canadian Research. TCPS has additional consent requirements for consent, storage of biospecimens, and research that involves genetic analyses.

If the protocol requires collecting biospecimens, the Board requires information on where and how the samples. The Board prefers to know the exact location of where the samples will be stored, but at a minimum the Board will need to know the country they will be stored.

For more information about the TCPS requirements please see:
https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2018.html

Special Considerations for Research Outside the U.S. and Canada

WCG IRBs will provide IRB review for research conducted outside of the United States and Canada in certain situations where the research will also have review by a local IRB, and for which there is a regulatory or funding requirement to have IRB review in the United States. Examples include Gates Foundation funded research conducted by PATH, and those for Compliance with the Brazilian regulatory requirement that externally funded research must have IRB approval in the country of funding, and other times on a case by case basis.

We do not provide IRB review of research in other countries where there is not a local IRB, including research for which it is unclear if local regulations require IRB review, such as stem cell research, device research, tissue collection studies, and questionnaires and surveys.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Special Consideration: Nursing Magnet Designation

WCG IRB has consistent membership and involvement by at least one nurse in the governing body responsible for the protection of human participants. A nurse Board member is always present and in voting status when a nursing protocol is reviewed. Our records indicate that the majority of our meetings have either a nurse member or nurse alternate member present and in voting status.

WCG IRB may also be asked to determine research to be exempt from IRB Review. Exempt determinations are made by a WCG IRB Board member. After discussion with Ms. Jan Moran, ANCC, she agreed that this is appropriate review under the IRB regulations, and that a nurse Board member is not required to make an exempt review determination.

Special Considerations for single patient expanded access / Compassionate use

When appropriate - and with approval from FDA, the manufacturer and an IRB - patients with no other options 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 IRB provides single patient expanded access reviews at no charge.

For review of single-patient expanded access

The WCG IRBs do not charge for review of single patient treatment use of a drug or device.

FDA maintains a 24-hour phone number for questions about emergency and compassionate use: Office of Crisis Management & Emergency Operations Center: (866) 300-4374.

The Process for Single-Patient Expanded Access Requests (Drugs/Biologics)

Single-patient expanded access requests are processed differently, using the following process:

- Please submit FDA Form 3926, the same form that is submitted to the FDA to request the single-patient IND, as well as other appropriate submission forms (HRP-280 for emergency use, HRP-282 for other single-patient expanded access).
- In accordance with FDA guidance, the request can be reviewed by an IRB Chair and does not need to go to the full IRB. Responses to complete single-patient expanded access review requests are usually returned within 24 to 48 hours of receipt.

- Because there is no protocol sponsor, WCG IRB does not charge a review fee for single-patient expanded access review – there is no additional burden on the patient.
- For questions about submitting single-patient expanded access requests, please contact clientservices@wcgirb.com.

WCG IRB does not provide review for pre-approval access to investigational products that do not follow the FDA's Expanded Access process.

Additional Resources

In 2019, the FDA created Project Facilitate, a pilot project to assist physicians and patients with understanding and negotiating the process of expanded access for oncology products.

The FDA has created a Q&A document with information about treatment use for investigational products.

Expanded Access for Medical Devices

The process for obtaining approval to use an investigational medical device outside a clinical trial is very similar to that for obtaining an investigational drug or biologic. For devices, single or small treatment group access is called Compassionate Use, whereas the process for a large treatment group is referred to as a Treatment IDE (Investigational Device Exemption).

The IRB review process for single patient compassionate use requests is the same as for single patient expanded access for drugs. The following WCG IRB forms should be used for submission of these requests:

- EMERGENCY USE OF AN INVESTIGATIONAL DEVICE (HRP-281)
- COMPASSIONATE USE OF AN INVESTIGATIONAL DEVICE (HRP-283)

For questions about submitting investigational medical device requests, please contact clientservices@wcgirb.com.

Additional References

Emergency Use of an Investigational Drug or Biologic - Information Sheet
Expanded Access to Investigational Drugs for Treatment Use — Questions and Answers
Expanded Access: Information for Physicians
FDA's Guidance on IDE Policies and Procedures, Expanded Access for Medical Devices

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

IRB Transfers

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

Required documentation for an IRB transfer review request

- Initial Review Submission Form (available on the Forms page
- Background information provided on the WCG IRB Form IRB Transfer Cover Letter Checklist & Summary
- Any documents that the submitter has been instructed to provide based on his/her answers to the questions on the IRB Transfer Cover Letter Checklist & Summary form (for example, the form instructs the submitter to provide any new risk or benefit information that was not submitted to the previous IRB)
- A copy of the complete current protocol if not already on file at WCG IRB
- 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 IRB Transfer Cover Letter Checklist & Summary form (for example, the form instructs the submitter to provide any new risk or benefit information that was not submitted to the previous IRB)

IRB transfer fall into two categories

"Active" - some or all participants are on active* treatment and the site may recruit more participants for the study

"Follow-up only" - the site will not recruit any more participants, but still has participants in follow-up (participants no longer on active* treatment)

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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

If a site is still enrolling and/or has active participants, WCG IRB will provide the site with an updated consent form with instructions for how participants can contact WCG IRB if they have questions about their rights as a research participant or with questions, concerns, input, or complaints about the research. Alternatively, if the site’s participants are all in “follow-up only” status, WCG IRB 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 participants notifying them of the change of IRB.

Recommended instructions for institutions deactivating their IRB or transferring multiple projects to WCG IRB:

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

The Review Process: Board Actions

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

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 WCG IRB 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 through an Approval letter (COA).

Outcome Documentation:

Once your study has been reviewed, we will prepare and send the outcome documents to you and all designated contacts (via WCG IRB Connexus, WCG IRBNet or WCG Velos), including:

- Certificate of Action (this will convey the Board's action as well as any special Board determinations, requirements, or other necessary information).
- Copy of the Board-approved consent form (when applicable), ready for use.
- Description of the changes to the consent form (depending on the type and extent of the Board's changes)

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:

You will receive written notification of the conditions promptly after the review.

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.

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.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Disapprove

"Disapprove" means the submission does not meet the criteria for approval and the IRB considers the research to have extensive deficiencies. Disapproval may occur for a variety of reasons, most of which involve participant safety and/or scientific validity. Disapproval is communicated to the investigator by letter, in which the reasons for disapproval are explained.

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.

Reconsideration of a disapproval decision may be requested. 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.

Defer

"Defer" means the IRB determines that the submission does not meet the criteria for approval and also does not meet the criteria for "Disapprove". The board takes a 'deferred' action to remove an item from board consideration at a scheduled meeting and obtain additional information or clarification. When the IRB takes this action, it will summarize its reasons and recommendations, if any.

When the board takes a "defer" action on a change in research, the change cannot be implemented, and the board expects the research will continue as previously approved.

Staff and/or board members follow up as directed with the investigator or sponsor to address the reasons for deferring the item. Reconsideration of a deferral may be requested. 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.

Staff prepare the item and reschedule it for the board to complete its review.

Incomplete submissions and inaccurate information. If answers on the WCG IRB 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.

Pull

The board may "pull" an agenda item at the request of the submitter, WCG IRB 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.

Changes to Research/ Additional Document Submissions

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

Submit a change in research review request via WCG IRB Connexus, or use the WCG IRB Change in Research Submission Form available on the Download IRB Forms page of WCG IRB to submit via one of our partner tools (IRBNet, WCG Velos, etc.).

COVID-19 Related Changes to Research

The WCG IRB has received questions from several research sponsors about the appropriate process for making changes to clinical studies in response to the COVID-19 epidemic. These changes may include things like:

- Decreasing the number of protocol-mandated in-person study visits to healthcare facilities
- Replacing protocol-mandated visits to healthcare facilities with home visits or telemedicine, allowing blood draws at remote or commercial laboratories
- Shipping investigational products directly to research participants

We want to provide information on the requirement for IRB review of changes in research made in response to this situation.

The FDA regulations require that:

Each IRB shall … (a) Follow written procedures for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without

IRB review and approval except where necessary to eliminate apparent immediate hazards to the human participants. 21 CFR 56.108(a)(4).

If a sponsor or investigator needs to make a change to research plans in order to eliminate apparent immediate hazards to research participants, these changes can be made and then reported to the IRB within 5 days, as per WCG policy. Eliminating immediate hazards may include actions to reduce potential exposure to COVID-19, or to continue to provide medically necessary study care (including study drug) to participants who have been placed in isolation or quarantine because of suspected or known exposures. WCG encourages sponsors and investigators to take such steps as necessary to eliminate apparent immediate additional risks to participants.

The notification to the IRB may be a full protocol amendment, but it does not have to be. The notification of the change in research (CIR) plans may also be a memo, letter, or other document that explains the changes being made, and provides enough information for the IRB to assess the relative risks resulting from the changes. The amendment or CIR document will proceed through IRB review as per the usual process.

If you have questions, please contact your WCG IRB representative, or Client Services, and they will be able to connect you with a member of our regulatory, medical or compliance teams as needed.

Changes to Research: 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 WCG IRB-approved consent form with the proposed changes clearly marked (if applicable).

A consent form modification

Requests for consent form modifications should be submitted via a change in research request created in WCG IRB Connexus, or use the WCG IRB Change in Research Submission Form available on the Download IRB Forms page of WCG IRB to submit via one of our partner tools (IRBNet, WCG Velos, etc.) You'll be prompted to submit a copy of the current WCG IRB-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 WCG IRB approved consent form. In order to facilitate the submission of consent form changes, WCG IRB now routinely provides sponsors and CROs with a clean copy of each

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

WCG IRB-approved consent (without site specific information in it). Changes sent to WCG IRB on the *sponsor's* template consent form will not be accepted.

WCG IRB 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 WCG IRB's electronic workflow system.

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

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

Investigators who provide instructions for use of a consent form other than the one already approved by WCG IRB 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.

Because sponsor version dates or numbers listed in headers or footers of consent forms are not an IRB requirement, but are voluntary information listed on consent forms, WCG IRB does not routinely update the information listed unless the submitted consent form indicates that information should be updated. WCG IRB uses an IRB versioning method to track the IRB-approved versions and content. We have observed that the consent form version identifiers used by sponsors, CROs, and institutions vary across the industry. As a general rule, the IRB will not proactively make any changes to sponsor/CRO or institution versioning, but instead we follow the instructions provided by the submitter.

How to Request a Reconsideration:

Items disapproved by the Board can be reconsidered upon written request. The request must include a rationale for the reconsideration. Additional information may allow the Board to favorable respond to the request. There is no additional fee for the reconsideration of disapproved items. Reconsiderations of Board-directed modifications do not incur additional fees if the requests concern 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.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

A Change of Principal Investigator

Please note that if the current investigator has not been overseeing the study, WCG IRB 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 Board requires written confirmation from the sponsor that the change is acceptable and has been approved as the sponsor is required to select investigators per 21 CFR 312.53(a).

If you submit via WCG IRB Connexus, submit it as a change in research, but select "Change in Investigator" when that option appears; submitters using IRBNet or WCG Velos should complete and submit our initial review submission form.

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

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 WCG IRB protocol and study numbers.

Additional Changes which require submission to WCG IRB

Contact Updates

When research is submitted to us for review in one of our portals (WCG IRB Connexus, IRBNet, WCG Velos) the submitter defines who on their team will have access to the outcome documents in the portal - adding and removing access over the life of the research as appropriate.

WCG IRB can also list a limited number of research team contacts in our internal system, and those distribution contacts are listed on the last page of each Certificate of Action; when a distribution contact listed on the Certificate of Action or a Continuing Review Report Form recipient changes, submit those requests for changes via our **Contact Information Update form**

available on www.wcgirb.com. Submitting the Contact Information Update form ensures the IRB has the correct contacts in the IRB's internal system for notifications or questions.

Administrative changes

Request review of increases in the number of participants allowed at the specific investigator site if a consent form change is needed.

Minor administrative changes sent to the investigator from the sponsor should generally be submitted to WCG IRB 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 WCG IRB. If you are in doubt about submitting a particular item, call Client Services at 855-818-2289 or e-mail clientservices@wcgirb.com.

Participant Recruitment Materials (Ads, etc.)

Request review of new or revised subject materials or advertisements via WCG IRB Connexus, or you may use the WCG IRB Change in Research Submission Form available on the Download IRB Forms page of WCG IRB to submit via one of our partner tools (IRBNet, WCG Velos, etc.) Print ads should be submitted as closely as possible to how 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.

WCG IRB 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 participants 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 WCG IRB 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 participant recruitment materials or other participant materials (diaries, questionnaires, etc.) that have been previously reviewed by WCG IRB, state in the cover letter that the items have been previously reviewed. Our 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* participant.

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

To avoid unnecessary additional production costs due to re-work, it is strongly recommended that WCG IRB 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 us for review, we pre-review the script and, if acceptable, approve 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 for final approval before use with participants and MUST match the approved script. Submit a copy of the corresponding script when you send the recording to us 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 unduly influential, incorrect, or out of compliance, 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: WCG IRB review requirements for web content are dependent on the type of content in question -

ClinicalTrials.gov and similar 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, WCG IRB will review submissions of such content. FDA Guidance regarding use of media advertising to recruit participants can be found at http://www.fda.gov/oc/ohrt/irbs/toc4.html#recruiting.

Website content can be reviewed either in relation to a specific protocol or as generic recruitment material. (See Generics.) 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 WCG IRB receives a request to close the file.

Content on websites and changes made to approved website content should be submitted for Board review **before they are posted to the web**. The website owner is responsible for receiving approval before using that content for recruitment.

Participant recruitment content on sponsor, investigator, or Site Management Organization websites requires IRB review. Only the content relevant to research should be submitted for review. Submit to us only website content which provides information to potential participants about research participation, as well as information about specific studies that WCG IRB 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.

It may be appropriate to request WCG IRB review of these materials as "generic" recruitment materials (See Review of Generic Material). The content should not be posted until WCG IRB has approved it.

WCG IRB 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.

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Recruitment material: Criteria for Approval of Advertising

- No statement or implication of a certainty of favorable outcome or other benefits beyond what is in the consent document and protocol
- No exculpatory language
- No emphasis on payment or the amount to be paid, by such means as larger or bold type
- No promise of "free treatment" when the intent is only to say participants will not be charged for taking part in the research
- Limit the information to what the prospective participants need to determine their eligibility and interest

Additional criteria for clinical trials

- No claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with FDA labeling
- No use of terms, such as "new treatment," "new medication," or "new drug," without explaining that the test article is investigational
- No inclusion of compensation for participation to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing

Requirements for Screening Materials

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

Introductory Statement:

- The screening script should include an introductory statement that informs the participant 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 participants of the sensitive nature of the questions that might make the participant 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; that is, collect the name and other identifying information at the end of the conversation and the form.

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 participant of whether they have met the preliminary screening requirements.
- The script should address in a closing statement whether the information received from the participant 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 participant as well, and the participant must have an opportunity to decline.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 an explanation of how they will be explained to the participants.
- We realize that the script may not be followed verbatim, as participants may ask additional questions or stray from the topic. This is acceptable, but we expect that the interviewer will keep as closely as possible to the spirit and letter of the script.
- It is useful to us if the investigator informs us of the use of the recruitment screen; such as, if it is going to be used with participants calling in from advertisements, for calling patients listed in a database, or for conducting cold calls.

Review of "Generic" Materials

"Generic" materials include items that an investigator wishes 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

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

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 in these forms. General research participation information will often be included, with a listing of types of research the investigator is conducting.

Accordingly, prospective participants should not have current treatment or medications adjusted, undergo a washout, or have a biopsy as a generic pre-screening activity. In those cases, the participant should be fully consented for the related protocol before beginning that protocol's screening activities.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Generic Advertisements

WCG IRB 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 participants 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 "participants will be paid for their participation" is recommended instead.

Expiration and Renewal of Generic Materials

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

IRB Reporting Requirements

Submit promptly reportable information via WCG IRB Connexus, or you may use the WCG IRB Promptly Reportable Information Form available on the Download IRB Forms of Wto submit via one of our partner tools (IRBNet, WCG Velos, etc.).

1. New or increased risk
2. Protocol deviation that harmed a participant or placed participant at risk of harm
3. Protocol deviation made without prior IRB approval to eliminate an immediate hazard to a participant
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 participant complaint

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

9. Suspension or premature termination by the sponsor, investigator, or institution
10. Incarceration of a participant 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 WCG IRB.

Please note, only INDs that prompt a change to the protocol or consent document are required to be reported to the IRB. We have based our guidance on the most current FDA recommendations, and it is our goal to try and encourage submission only of the items required and to avoid submission of non-reportable events, which causes delays in review and detracts from our mission of human participant protection. The FDA Guidance states the following:

> "In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood."

When safety reports are submitted to WCG, if additional action/information is required, you will be contacted within 30 days. Otherwise, please consider this information filed only with no additional formal acknowledgment or confirmation.

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 participants to WCG IRB in a timely manner:

- Upon request, a copy of the written plan between Client and Site that addresses whether expenses for medical care incurred by Human Research participants 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.
- Any site monitoring report that directly and materially affects participant safety or their willingness to continue participation. Such reports will be provided to the Review Board within 5 days.

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

Planned Deviations

Please note that planned deviations should be submitted to WCG IRB 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 WCG IRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human research participants [(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 participants or the integrity of the research data should be submitted to WCG IRB for review and approval prior to implementation except where necessary to eliminate apparent immediate hazards to the human research participants [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].

These different requirements regarding planned protocol deviations are necessary because 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).

Investigator Noncompliance

WCG IRB expects PIs to conduct research activities in accordance with the IRB's requirements, as set forth in this Guide and in compliance with all federal, state, and local regulations. We define investigator noncompliance as the failure to follow the applicable regulations and/or the requirements and determinations of the IRB.

Examples of Noncompliance

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

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 participant 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 participant or placed participant 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 participant'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 the IRB to indicate potential noncompliance, the 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 the IRB 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 Board.

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Suspensions and Terminations

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

- When research is not conducted in compliance with federal, state, and local requirements and in accordance with our requirements, or
- When the risk-to-benefit ratio no longer justifies continuing the study (based on information received by the IRB related to safety or other unanticipated risks to research participants 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 participant. Additionally, if the suspension or termination is for investigator noncompliance, we reserve the right to initiate immediate review of all the PI's active studies.

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

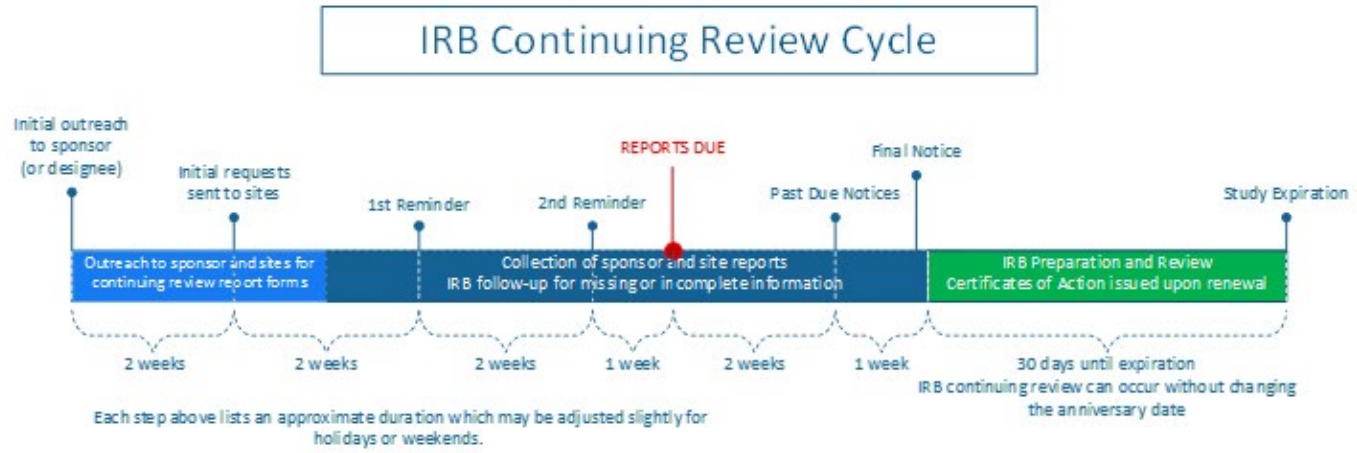
In accordance with federal requirements, suspensions or terminations of previously approved research or investigators are reported by the IRB to the sponsor and to the appropriate regulatory authorities

Overview of continuing review activities and required reports

During the initial review of a protocol, the Board makes a determination regarding 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 review more frequent than annually for other research as deemed appropriate.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com



Contacts for Continuing Review Form Notifications

For new initial review site submissions, all site level contacts receive notification when the site level continuing review report form is due.

For new initial review protocol submissions, all sponsor and CRO contacts receive notification when the protocol level continuing review report form is due, if one is required.

Although notifications regarding the continuing review reports will be sent to multiple contacts, please only submit one completed copy. Multiple copies can result in unnecessary follow-ups by our staff for clarification.

Site Reporting

Completed Continuing Review Report Forms (CCRF) provide the IRB with the study-related data necessary to monitor the progress of the research at sites. Identifying information including investigator name, sponsor name, protocol number and the "sequence" number of the form is listed at the top of each form. The CRRF is sent out approximately 86 days before the study's expiration date, in order to ensure it is completed and sent back to us before the Board conducts the study renewal review. The Board may take action to suspend or terminate approval of the research if a report is not accurately completed and returned promptly.

CRRFs must be filled out completely and returned to us approximately 56 days before the study expiration date. This time frame allows for IRB staff to review the completed form, follow up if they have questions, and send it to Board with the study renewal review. If we have not yet

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

received a completed report form, two "Reminder Notices" are sent out; one at about two weeks and another about four days prior to the due date of the form.

Even if the site has not started enrolling participants, the site must complete the CRRF and return it to WCG IRB before the due date printed on it, to inform the Board of the study's status at the site.

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

Sponsor Reporting

Before each annual review, WCG IRB sends out a Continuing Review Report (PCRR) to the sponsor or CRO contact that we have on file. The PCRR 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 ask that you complete and return the PCRR before the due date indicated on the form. The individual study sites will continue to receive separate site progress reports to complete and submit as well.

WCG IRB aims to make the PCRR process as efficient as possible for all parties. Therefore, WCG IRB will accept receipt of the completed PCRR 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. WCG IRB is flexible as to the format in which this information is received and will accept other reports that provide the same basic information.

The PCRR is sent out approximately 100 days before the protocol's expiration date and are due approximately 56 days before the expiration date in order to ensure it is completed and sent back to WCG IRB before the Board conducts the continuing review of the study. If we have not yet received a completed report form, two "Reminder Notices" are sent out; one at about two weeks and another about four days prior to the due date of the form. The Board may take action to suspend or terminate approval of the research if a report is not accurately completed and returned promptly.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Delinquent Progress Reports

WCG IRB will continue to follow-up with the investigators, sponsors and CRO contacts to facilitate timely receipt of a continuing review reports. If a completed form is not received by the due date, approximately 10 days after the due date, a “past due” notification is sent

The Board may take action to suspend or terminate approval of research if reports are not accurately completed and returned promptly. If WCG IRB suspends or terminates the study, at a minimum, the investigator and sponsor will be notified of the Board’s action.

If the Board suspends the research, WCG IRB is required to report the suspension to the appropriate federal agency or agencies (for example, FDA and/or OHRP.) If the suspended investigator is at an institution which has notified WCG IRB 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 WCG IRB.

Definition of Screen Failures and Withdrawals

Report the number of screen failures and withdrawals on the Site Continuing Review Reports according to the following definitions. WCG IRB acknowledges that the definitions for these terms vary across the industry, but please apply the following definitions when reporting to WCG IRB:

- Screen failure: Participant(s) removed from the study during the screening process because they did not meet all inclusion and exclusion criteria, or other requirements that must be met for research participation. Participant(s) who leave the study after randomization or assignment to study treatment should be counted as withdrawals rather than screen failures, even if the participant did not start the study treatment.
- Withdrawal: Participant(s) are considered to have been withdrawn/discontinued from the research when the participant(s) either stopped participation or the research team stopped the participant's participation early for reasons other than reaching a study endpoint. Do not count screen failures when reporting withdrawals.

Study Renewal vs. Closure

Sites receive a WCG IRB Site Continuing Review Reports when the expiration date is approaching. The Board may conduct the study continuing review up to 30 days prior to the

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

expiration date listed on the Approval letter. **Review fees apply for the continuing review service** and review is carried out unless WCG IRB receives a study closure notice *prior to the Board's renewal review.* If a closure notice is received by WCG IRB before the expiration date, but after the Board's continuing review, the site will still be billed for the renewal review. To avoid unnecessary reviews and fees, do not delay reporting a study closure to WCG IRB 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 or after the expiration date. For example, if the study's expiration date is 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, an Approval letter is forwarded to the investigator and other study contacts as applicable. The Approval letter states "Approval includes: Study and Investigator for an additional continuing review period. This approval expires on the date noted above." Approval of the study encompasses renewal of the protocol, all previously approved amendments or revisions, and the existing consent and study materials as previously approved.

If, at the time of renewal, the Board determines that a modification to the consent form is necessary, the Approval letter will indicate approval of a consent form and will be accompanied by a revised consent form.

Study Closure

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

1. All participants have finished all protocol related interventions, interactions, final visits and follow-up; and
2. The sponsor representative reports the study is closed at your site or permanently closed to enrollment
3. If the study was conducted under a Federalwide Assurance for research participant to federal oversight other than FDA: No additional identifiable private information about the participants is being obtained and all data analysis at the site is completed.

WCG IRB will close the study upon receipt of the closure report. A Closure Report Form is available at www.wcgirb.com .

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

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

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)).

WCG IRB conducts the following types of site visits:

- For-Cause - WCG IRB staff initiate "for-cause" site visits in response to concerns raised about the site, investigator, etc. These visits are usually carried out by WCG IRB Regional Representatives, Board members or WCG IRB 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 WCG IRB Regional Representatives, Board members or WCG IRB management.

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 WCG IRB site visit, please consult the current fee schedule.

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

Fees

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

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

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Research Review fees at WCG IRB fall into four general categories:

Initial Review of the Research.

Initial review encompasses the review of the research protocol, one associated consent form, 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.

Additional fees are required for the review for an investigative site, if teleconference or videoconference with the site is necessary to complete the initial review, if multiple consent forms are submitted, and if translation of consent forms and other participant materials are necessary.

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

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. 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.

Changes to Research:

Modifications to research which require 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. The change in research fee applies each time review and preparation of regulatory documentation is required for a research site.

Miscellaneous:

WCG IRB bills additional fees for services such as translations and acknowledgements. We may charge a fee for submissions not made via the WCG IRB Connexus or IRBNet portals

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Reconsiderations

In accordance with 21 CFR §56.109(e) and 45 CFR §46.109(d), WCG IRB 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. There is no fee for the review. Requests for reconsideration and supporting materials may be directed to the WCG IRB 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 WCG IRB and ask for reconsideration; however, we advise you not to delay complying with the Board's instructions.

WCG IBC Services

Human gene transfer (HGT) is a growing, promising area of medical research studying drug products that incorporate engineered or artificial DNA or RNA. Clinical trials involving HGT products must meet the specific oversight requirements found in the NIH Guidelines for Research Involving Recombinant and Synthetic Nucleic Acid Molecules (NIH Guidelines).

Before clinical research subject to the NIH Guidelines can begin, it must be approved by an NIH-registered Institutional Biosafety Committee (IBC). IBCs ensure that research with potentially biohazardous agents is conducted according to the NIH Guidelines and current best biosafety practices.

Why Choose WCG IRB for IBC Review?

WCG IBC Services provides the experience, personalized service, and streamlined process you need for efficient, safe, and compliant oversight of gene transfer research. With a dedicated WCG IRB team partnering on your review and remote IBC meetings scheduled on demand, we're committed to providing an efficient and thorough turnaround for each review.

Our experts have extensive experience in all aspects of site startup for human gene transfer research and are ready to answer your questions, including:

- Is my research subject to the *NIH Guidelines*?
- How can I prepare for a multicenter trial involving human gene transfer research?
- Which sites are best prepared to start enrolling subjects as soon as possible?

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

- How does WCG IRB register an IBC on behalf of a new site?
- What are the requirements for IBC approval?
- What are best practices for transportation, storage, administration, and disposal of genetically modified products?
- What are the timelines associated with IBC review for different types of studies?
- How does WCG IBC Services work in tandem with IRB review, site selection, contracting, and billing?

For Clinical Trial Sponsors and CROs

Most drug products that incorporate engineered DNA or RNA qualify as human gene transfer products. Our experts can help you determine whether your clinical trial requires IBC review and review prospective site lists to advise on the best startup approach for each site requiring IBC review.

We recommend that sponsors and CROs contact WCG IBC Services during the project planning phase to discuss:

- Timelines and enrollment dates
- Applicability of NIH Guidelines and IBC review requirements
- Document preparation (protocol, investigators' brochure, pharmacy manual) for IBC review
- Qualification of prospective site list (identification of sites that are in-network or that require registration)
- Distribution of study documentation to sites

For Research Institutions

Our IBC network includes nearly 400 active sites, ranging from small clinics to community hospitals and major academic medical centers. Our review teams work closely with clinical coordinators and investigators at each site to learn about your needs and concerns and advise on best practices for safety and compliance.

For each new study at your site, we provide a customized biosafety standard operating procedure (SOP) and walk you through the steps required to get to IBC approval. IBC operations are transparent and interactive and allow sites to fully understand and direct compliance activities related to gene transfer research.

1019 39th Ave SE / Suite 120
Puyallup, WA 98374
855-818-2289
www.wcgirb.com

Coordinating IRB and IBC Reviews

Clients that utilize both WCG IRB and WCG IBC Services reap greater synergies as smoother communications between our IRB and IBC teams accelerate both review processes.

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 the IBC administration and review page on the WCG IRB website for more information.

Disclaimer

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