HANDBOOK FOR QUORUM REVIEW IRB

Contents

INTRODUCTION

The Mission of Quorum Review IRB

The mission of Quorum Review IRB (Quorum) is to safeguard the rights and well-being of research participants while enhancing the clinical research process. Quorum Review IRB provides ethical review of clinical research according to the principles of the Belmont Report, and operates in accordance with regulations and guidelines set forth by the United States Food and Drug Administration (FDA), the Department of Health and Human Services, Office for Human Research Protection (HHS/OHRP), Health Canada, and the International Committee on Harmonisation (ICH), as applicable.

The Scope of Quorum Review IRB's Authority

National, state, provincial, and local authorities set forth the standards for the composition, operation, and responsibility of ethics boards that review clinical research. An Ethics Review Board - also known as an institutional review board (IRB), a research ethics board (REB) or an independent ethics committee (IEC) - has the authority to approve, disapprove, require modifications of, or place restrictions on research. Quorum Review IRB operates within the requirements of the authorities mentioned above and maintains written procedures for the review and continued oversight of research trials.

Statement of Compliance

Quorum Review IRB conducts review in accordance with pertinent authorities, including, but not limited to, the ICH Guidelines for Good Clinical Practice, US Food and Drug Administration (21 CFR Parts 50 and 56), US Department of Health and Human Services (45 CFR Part 46), the Canadian Food and Drug Regulations (Part C, Division 5), Part 4 of the Canadian Natural Health Products Regulations, the Tri-Council Policy Statement (TCPS), the ethical principles outlined in the Belmont Report, and the principles of the World Medical Association Declaration of Helsinki.

Quorum Review IRB is registered with the United States Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) with registration number IRB 00003226. Quorum Review IRB is also fully accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP). Verification of AAHRPP accreditation can be obtained on the AAHRPP website located at http://www.aahrpp.org

As a research ethics board, Quorum Review IRB is appropriately constituted, organized, and operated in accordance with regulations and guidelines referenced above, to the extent they apply. Quorum Review IRB also complies with other national, state, provincial, and local laws such as the US Health Insurance Portability and Accountability Act of 1996 (“HIPAA Privacy Rule”), the Personal Information Protection and Electronic Documents Act (PIPEDA), and other relevant authorities in jurisdictions that relate to clinical research in which Quorum Review IRB provides oversight.

Quorum Review IRB Handbook

The Handbook provides a guide for using Quorum Review IRB as an Ethics Review Board. It contains policies, procedures, sample forms, and guidelines to be used in preparing materials for Board review, as well as information on managing ongoing research activities, continuing review, and closing. Periodic revisions to this Handbook will be issued to reflect changes in Quorum Review IRB's policy or government regulations. Handbook revisions will be posted promptly within Quorum Review IRB's OnQ Portal at www.QuorumReview.com, where the most recent version of the Handbook can be found. If you do not have an OnQ Portal account please contact Initial Study Support at Quorum Review IRB.

Who Should Use This Handbook

This Handbook is designed for investigators and their staff, as well as sponsors, contract research organizations (CROs), and site management organizations (SMOs). References to “sponsors” in this Handbook should be read to apply also to CROs and SMOs that act on behalf of sponsors.

Contacting Quorum Review IRB

Quorum Review IRB's main office in Seattle can be reached by telephone at (206) 448-4082. In order to expedite your call, please have the protocol number, investigator's name, and/or Quorum Review IRB number (“QR#”) available. The QR number generally is located in the bottom corner of approval documents.

Quorum Review IRB's staff is available at the main office in Seattle to support Canadian sites and research. Although Quorum Review IRB has an office in Canada, please send all submissions to the main office.

Quorum Review IRB has four primary teams to provide customer support: the Client Support Team, Study Management, Client Relations, and the Initial Study Support Team.

- The **Client Support Team** is a call center available to answer questions from research sites. Typical issues include inquiries regarding a site's approval status, notifying Quorum Review IRB of changes in staff, and assistance regarding safety reporting. French- and Spanish-speaking assistance is available.
- An **Account Manager** will be assigned to your study and serve as the primary protocol-level contact. The Account Manager is available for protocol-level questions, comments, or concerns.
- **Client Relations** is available to answer questions regarding Quorum's services and capabilities, general questions and/or discuss concerns or complaints.
- **Initial Study Support** is available to assist customers in submitting a protocol for initial review.

Quorum Review IRB Contact Information
Mailing Address for US and Canadian studies 1501 Fourth Avenue, Suite 800 Seattle, WA 98101

Quorum Review IRB Contact Information	
Telephone	US: (206) 448-4082
Toll Free	(877) 472-9883
Fax	(206) 448-4193
Hours	
Initial Study Support:	5:00 a.m.-5:00 p.m. Monday-Friday
Client Support Team:	5:00 a.m.-5:00 p.m. Monday-Friday
Other Business Hours:	5:00 a.m.-5:00 p.m. Monday-Friday (All times are Pacific Time)
Staff E-mail:	
Generally, FirstInitialLastName@QuorumReview.com (for example, John Smith's email would be JSmith@QuorumReview.com)	
Initial study submission questions by e-mail:	InitialStudySupport@QuorumReview.com
General questions by e-mail:	ClientRelations@QuorumReview.com
Other Quorum Sites	
Cambridge, MA:	One Broadway, 14th Floor Cambridge, MA 02142
Vancouver, BC:	World Trade Centre, 999 Canada Place Suite 404 Vancouver, BC V6C 3E2

Quorum Review IRB Website and OnQ Portal

Customers can also contact Quorum Review IRB, download documents, and submit materials using Quorum Review IRB's website, located at www.QuorumReview.com. The website includes:

- Electronic versions of all forms for use during a study
- Guidance for submitting materials for Board review
- The Quorum Review IRB OnQ Portal, a secure web portal for submitting or retrieving documents
- General information about Quorum Review IRB
- Tips on working with Quorum Review IRB
- A customer feedback page
- Resources and information for research participants

The Quorum Review IRB OnQ Portal is password-protected and available to study contacts at the site and sponsor level. Please contact Quorum Review IRB to learn more about this service or to request a portal account. Users can view, download, and print all Quorum Review IRB approval documents and most other Board correspondence. The OnQ Portal also offers a status report for tracking site submissions from initial review through the Board's final decision. Users can submit materials for review electronically and securely through the OnQ Portal provided that the submission is not larger than 15 MB. For items that are larger than 15 MB either use a compression utility such as WinZip, email items that are less than 50 MB to InitialStudySupport@QuorumReview.com, mail or fax to the attention of Initial Study Support.

Suggestions

Quorum Review IRB welcomes your feedback. We strive continuously to improve our services and want to hear how we can do our job better. Please send any comments or recommendations for improvement to the Client Relations Team, the Client Support Team, or your Account Manager. Comments and suggestions may also be submitted via the “Contact Us” page on Quorum Review IRB's website.

WORKING WITH QUORUM REVIEW IRB

Roles and Responsibilities of the Principal Investigator and Sponsor

Quorum Review IRB expects investigators and sponsors to be responsible for the conduct of research studies at their research facilities consistent with the Board-approved protocol and applicable laws, regulations, and guidelines such as the ICH Guidelines, the ethical principles of the Belmont Report, the Tri-Council Policy Statement (TCPS 2; applicable in Canada) and the FDA, DHHS/OHRP, and the Food and Drug Regulations of Health Canada. An investigator also is responsible for understanding and upholding any state and provincial laws applying to research (for more information, see the section below titled "State and Provincial Law").

When an investigator signs the submission documents, s/he assures that the research will be conducted according to the protocol as well as Good Clinical Practices (GCP) and that the investigator has made careful consideration of the study before deciding to participate. In following the guidelines of GCP, the investigator should be aware of obligations under GCP Section 4 (ICH-E6) as they apply to:

- Investigator's Qualifications
- Adequate Resources
- Delegation lists of appropriately qualified staff
- Medical Care of Trial Subjects
- Communication with the Review Board
- Compliance with the Protocol
- Investigational Product(s)
- Randomization Procedures and Unblinding
- Informed Consent of Trial Subjects
- Records and Reports
- Progress Reports
- Safety Reporting
- Premature Termination/Suspension of a Trial
- Final Reports by Investigator

The investigator is held accountable even if a sponsor, CRO, SMO, or designee has assisted the investigator in completing the submission documents or if the submission document is unsigned because it was submitted via the OnQ Portal. Quorum Review IRB expects that the investigator has evaluated the proposed research for risks and benefits and that the investigator finds merit in the research design for each protocol, regardless of whether the research was designed by the investigator or a sponsor. It is expected that investigators will only use test articles in accordance with the current Board-approved protocol and under the appropriate controls set forth in federal regulations, including 21 CFR §312 and §812. Investigators must also follow the data safety monitoring plan outlined in the protocol as applicable.

Investigators must maintain the qualifications necessary to oversee the research. To be qualified, investigators must maintain proper medical licensure and not have limitations imposed by state licensing

authorities or regulatory agencies (such as the FDA, Department of Health and Human Services, or Office of Human Research Protection) that restrict the ability to conduct research activities. Investigators are required to promptly report any adverse actions against their licensure or ability to conduct research. Investigators must also maintain adequate resources to conduct the research. This means setting aside enough time to properly conduct and complete the trial as set forth in the protocol and maintaining adequate facilities and equipment to conduct the protocol properly and safely. Furthermore, investigators must have adequate research staff that is appropriately trained regarding their research-related functions and regulatory responsibilities. It is important to note that although delegation of certain tasks and responsibilities to qualified staff is permissible, the investigator is ultimately responsible for the conduct of all research activities. This includes reporting of any changes in research activity in a timely manner and ensuring proper informed consent of research participants.

Investigators are also responsible for the proper storage of study drug and participant records (including documentation of informed consent). Both should be maintained in a secure area with access limited to appropriate research staff.

Prospective Board approval of all participant materials (including advertisements, telephone scripts and screening tools, gifts programs for retaining participants, and participant instructions) is required. Please note that some recruitment practices may require a separate HIPAA Authorization or a waiver thereof. For more information, see the section titled “HIPAA Waivers” below or visit Quorum Review IRB's website www.QuorumReview.com.

Sponsors and investigators must report Unanticipated Problems and events that occur during the study. Sponsors and investigators must also submit a “Site Status Report for Periodic Site Review” form as requested by Quorum Review IRB to ensure Board review before expiration. Investigators must submit a “Change Request Form for Sites” to indicate changes in study contact and site-specific fields on the consent form (changes to research facilities, contact information, or compensation). Sponsors must submit a “Central Study Information Change Request” form to Quorum Review IRB to indicate changes in study or billing contact. Finally, each investigator is expected to submit a “Site Status Report for Closing” form at the conclusion of the study.

Research Participants

The key relationship in any research trial is between the investigator and the participant. The investigator maintains the ultimate responsibility for interactions with the research participant throughout the study. An investigator must obtain each participant's informed consent before and throughout his or her participation in a study. In addition, investigators have a responsibility to communicate to participants significant new findings developed during the course of the study that may relate to their willingness to continue participating. As part of the investigator's responsibility to foster open communication with participants, the investigator must also be available to respond to questions or complaints from research participants about study procedures, their research rights, and whom to contact in the event of a research-related injury.

Sometimes, a research participant may desire to speak with a party that is independent from the research site. To that end, every Board-approved consent form provides information for research participants regarding how to contact Quorum Review IRB. Quorum Review IRB maintains designated

staff to receive research participant inquiries and complaints. French- and Spanish-speaking staff is also available to assist research participants. In some circumstances, it may be necessary for Quorum Review IRB to correspond with the investigator or the sponsor to obtain more information about an inquiry or complaint. While Quorum Review IRB may facilitate communication between the research participant and the investigator, please note that the investigator bears the ultimate responsibility to see that the participant's inquiry or complaint is resolved. Please also note that in the interest of privacy, Quorum Review IRB strives to preserve the confidentiality of information conveyed by research participants when requested and as appropriate.

Site Visits

During the course of the study, Quorum Review IRB may choose to conduct an on-site visit of an investigator's research facility. Quorum Review IRB may choose to visit a research site for a variety of reasons, including, but not limited to, observing the informed consent process, responding to a particular concern raised by the Board, addressing an issue raised by a participant complaint, or gaining a better understanding of the attributes of the local community. Quorum Review IRB also conducts routine site visits in accordance with Massachusetts state requirements.

Before the Visit
Quorum staff or the Board site visitor will contact the investigator to arrange a visit at a mutually agreeable time.
During the Visit
During a visit, the Board site visitor might interview the investigator and research staff, review study records and drug storage, or observe how informed consent is obtained from potential study participants.
After the Visit
After the visit has been completed, the Board will notify the investigator if any further action is required by the Board.

Conflict of Interest

Quorum Review IRB strives to follow industry standards for managing and minimizing potential conflicts of interest. Quorum Review IRB requirements for reporting conflicts of interest are based on the FDA regulations at 21 CFR 54 and the Public Health Service (PHS) regulations at 42 CFR 50, Subpart F. Please note that investigators may have obligations under the above-referenced regulations, local law, and/or Institutional policies to report conflicts of interest to their Institutions, the appropriate governmental agencies, and other parties. These requirements may differ from Quorum Review IRB’s reporting requirements. It is the investigator’s responsibility to ensure compliance with all applicable reporting requirements with respect to conflicts of interest. Quorum will accept reports of conflicts of interest that do not meet Quorum’s threshold for reporting, if institutional policies require reporting of such conflicts to the IRB.

Quorum Review IRB expects investigators to disclose potential conflicts of interest involving research staff or immediate family members (including spouses and dependent children). The financial and non-financial interests of investigators, staff and immediate family members that must be reported to

Quorum Review IRB are listed below. These criteria apply equally regardless of funding or regulatory oversight.

Conflicts that must be reported to Quorum Review IRB:

1. Financial arrangement based on outcome of the study: Any financial arrangement with the sponsor of the study, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. This includes compensation that could be higher for a favorable outcome than for an unfavorable outcome, such as compensation that is explicitly greater for a favorable result or compensation to the investigator in the form of an equity interest in the sponsor of a covered study or in the form of compensation tied to sales of the product, such as a royalty interest.
2. Significant Payment (exclusive of the costs of conducting research): Any significant payment of more than $25,000 from the sponsor to the investigator or institution such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, honoraria, or paid authorship during the time the investigator is carrying out the study until the study is closed with Quorum.
   This requirement is intended to mirror the FDA financial disclosure requirements of significant payments of other sorts (SPOOS); though FDA requires reporting of SPOOS for one year following the closing of the study while Quorum only requires reporting until the study is closed with Quorum. FDA has provided additional explanation of the definition of significant payments of other sorts (SPOOS) as follows: The $25,000 threshold amount for reporting SPOOS is based on the cumulative amount of SPOOS received by the investigator (including payments to the spouse and dependent children over the course of the study and for one year following completion of the study. If an investigator were given equipment of money to purchase equipment for use in the laboratory/clinic but not in relation to the conduct of the clinical study, payment would be considered a significant payment of other sorts. If however, the investigator were provided with computer software or money to buy software needed for use in the clinical study that payment would not need to be reported. Generally reasonable payments made to investigators to cover reimbursable expenses such as transportation, lodgings and meals do not fall within the definition of SPOOS, and therefore, would not need to be reported. When the research has been closed with Quorum for that site, the investigator is no longer obligated to report conflicts of interest to Quorum related to the specific research study. (FDA Guidance, Financial Disclosure by Clinical Investigators, February 2013, IV.C.4.-6.).
3. Intellectual property rights or proprietary interests: Any proprietary interest in the product tested in the study. This includes property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.)
4. Any significant equity interest in the sponsor of the study: “Significant equity interest” is defined as follows:
   1. For non-publicly traded corporations and other entities: any ownership interest, stock options, or other financial interests whose value cannot be readily determined through reference to public prices.
   2. For publicly traded corporations: any equity interest that exceeds $50,000 during the time the clinical investigator is carrying out the study and for one (1) year following completion of the study. Please note: The following does not need to be disclosed: any ownership or other interest, which is a sub-set of a mutual fund or other investment vehicle (for example a 401K or other non-actively managed retirement fund) that the individual has no control over and does not direct.
5. Employment or executive relationship: Any employment or executive relationship with the sponsor of the study. Please note that any payment amount over $10,000 in the past 12 months must be

disclosed.

6. Enrollment or recruitment bonuses or finder's fees: Any enrollment bonuses, finder's fees, and/or gift of equipment to the site or individual from the sponsor.
    1. Enrollment or recruitment bonuses policy: Generally, the Board views bonus payments for recruitment or enrollment activities offered by Sponsors to PIs as presumptively impermissible conflicts. However, bonus payments do not include per-participant payments made by Sponsors to accelerate enrollment (e.g., for additional advertisements). Enrollment or recruitment bonuses are incentives from the Sponsor to a PI or Site and may be either financial or non-financial based on the rate or timing of the recruitment. The Board deems enrollment or recruitment bonuses to research staff inappropriate and susceptible to creating inequitable selection of research participants. Payments that reimburse an individual at fair market value for his/her efforts and costs associated with the research may be acceptable.
    2. Finder's Fees policy: Quorum defines a finder's fee as financial or non-financial incentives paid from a PI or a Sponsor to a person who is not a member of the study staff, nor otherwise affiliated with the study who refers a potential participant. Generally the Board deems acceptable the provision of finder's fees to individuals who do not have a fiduciary relationship with the potential participant and who are not likely to create inequitable selection of research participants. An individual with such a relationship toward a potential participant would be in a position of trust or authority, such as a physician or parent. However, a finder's fee is not acceptable if it is found to interfere with providing prospective participants with sufficient opportunity to consider whether to participate or otherwise increase the possibility of coercion or undue influence on investigators or participants.
7. Other possible conflicts: Any other interest as defined by local law, institutional policy, or other factor that may create an actual or apparent conflict of interest that is not otherwise addressed above.

Investigators must complete Quorum Review IRB's Conflict of Interest Statement: Disclosure of Financial Interests and Management Plan if any of the above-described conflicts of interest exist. Please note that conflict of interest disclosure forms are reviewed by the convened Board.

The investigator must explain their plan for managing and minimizing any disclosed conflicts of interest. It is important for the Board to receive this management plan. Some possible actions the investigator can take to manage potential conflicts of interest include:

- Disclose the conflict in the consent form
- Complete additional training or education requirements for the investigator and study staff.
- Require a non-conflicted sub-investigator, monitor, or other study staff member to assist or conduct certain parts of the research such as the informed consent process
- Require a designee without a conflict to collect and report study data
- Modify the recruitment and retention plans to account for the existing conflict
- Divest financial interests either partially or completely

Change to Conflict of Interest Status
All changes to the conflict of interest status of an investigator, a member of the research staff, or an immediate family member that exceeds one of the thresholds listed (or further exceed a threshold already reported to the Board) must be submitted to Quorum Review IRB in a revised Investigator Conflict of Interest Statement.

If the Board does not find the management plan to be adequate, the Board might impose one or more of the protections listed above or take additional action. Please note, as a matter of policy, the Board

requires disclosure of reported conflicts of interest in the applicable consent form(s). This option is pre-selected on the Investigator Conflict of Interest Statement Form

During the identification, resolution, and management of conflicts, the Board will take reasonable steps to protect the specifics of any reported financial information but cannot guarantee confidentiality. Such information might be disclosed to a governmental agency or other parties, such as the sponsor, or CRO.sponsor auditor. Please note that failure to disclose possible conflicts of interest is a serious offense and could lead to suspension or termination of Board approval.

Investigator and Research Staff Education

The Board expects the investigator and research staff to be able to demonstrate comprehension and adherence to the pertinent laws and regulations, state, provincial or other local laws, pertinent records confidentiality provisions (including HIPAA if the investigator's site is a “covered entity” in the US) and the guidelines set forth in this Handbook throughout the conduct of a study. In addition, the Board expects that the investigator will engage in continuing education devoted to the protection of human research participants and ensure that the study staff is properly trained on human research participant protection.

In the absence of an industry or regulatory continuing education standard, the Board generally considers the following opportunities adequate:

- CITI Program: Course in the Protection of Human Research Subjects (an online program);
- National Institutes of Health (NIH) Clinical Center: Clinical Research Training (an online program);
- Seminar or online training specific to human research participant protection; or
- Self-study specific to human research participant protection.

Research-Related Injuries

Quorum Review IRB expects each consent form to include a section explaining whether or not compensation and/or medical care will be provided for injuries sustained during the research. The terms of this description must not be exculpatory. In other words, the description must not ask the participant to relinquish any rights the participant would otherwise have and must not release or appear to release the sponsor, investigator, or institution from liability.

In the event that a participant sustains a research-related injury, the sponsor and investigator are expected to act in a manner consistent with any policies outlined in the Board-approved consent form regarding medical care and/or payment. The investigator also should refer to the clinical trial agreement with the sponsor to determine who shall provide or pay for any needed medical care.

Investigator Noncompliance

The Board expects the investigator to comply with the Board-approved protocol, applicable laws and regulations, applicable ICH and other guidance, and Quorum Review IRB's policies outlined in this

Handbook or otherwise communicated by Quorum Review IRB. When an investigator fails to comply, the Board has a process for investigating, assessing, and determining investigator noncompliance. Please be advised federal regulations require Quorum Review IRB to report findings of serious or continuing noncompliance to the appropriate authorities, such as the FDA or OHRP. Allegations of noncompliance can arise from multiple sources, including research participants, research staff, Quorum Review IRB staff, a report of an Unanticipated Problem, licensing board, or the sponsor, CRO, SMO, or other entity.

The Board uses the following relevant definitions:

- Noncompliance: Refers to a failure to follow regulatory obligations and/or Board requirements or determinations.
- Minor noncompliance: An instance of noncompliance that has minimal impact on the safety, rights and welfare of participants or the integrity of the study (for example, filing a “Site Status Report” with the Board one day past due).
- Continuing noncompliance: A pattern of noncompliance that indicates a negligent disregard or gross indifference to compliance with regulatory obligations and/or Board requirements or determinations (e.g., failure to timely respond to repeated written requests for information about active participants).
- Serious noncompliance: An instance of noncompliance that results in increased risk to participants and/or significantly and adversely affects the safety, rights, and welfare of participants or the integrity of the study (e.g., falsification of data or significant modification to Board-approved protocol without prior Board review and approval).

Communication of Research Results

In some situations, findings from a research study indicate that current and past participants are at increased risk of a problem that was not anticipated at the time the study was designed. In such cases, current and past participants should be notified of the new finding. If such a finding is detected, the sponsor or site should submit a proposed communication to Quorum Review IRB for review and approval prior to dissemination (such as a revised consent form or a letter to participants).

Following the conclusion of Quorum Review IRB's jurisdiction for a study at a research facility, Quorum Review IRB encourages sponsors to have mechanisms in place to contact past participants and inform them of any significant new findings that may affect their health and well-being.

Quorum Review IRB encourages sponsors and investigators to publish research results and expects sponsors and investigators to comply with any regulatory obligation to do so.

Types of Clinical Research Reviewed by Quorum Review IRB

Quorum Review IRB reviews a broad range of clinical research in the United States and in most jurisdictions in Canada, including clinical research regulated by the FDA, OHRP, and Health Canada. Quorum Review IRB also reviews international research conducted outside the United States and Canada. Quorum Review IRB reserves the right to decline Board review of certain studies, such as prisoner research and planned emergency research. Please contact our Client Relations Team with any questions about Quorum Review IRB's ability to review a particular type of research or a specific protocol.

Some studies may be exempt from regulatory review requirements altogether. Please contact Initial Study Support if you would like Quorum Review IRB to conduct an exemption determination.

Expedited Research

Quorum Review IRB provides Expedited Review of research when requested by the Sponsor and when the research is minimal risk and qualifies under one or more of the seven expeditable categories that apply to initial review of research. Please see the section titled "*Expedited Review*" for more information.

Federally Funded Research

Quorum Review IRB provides review of federally funded studies in the United States, including studies that are regulated by HHS/OHRP. These studies are subject to additional submission and review requirements. Please see the section titled "Federally Funded Studies" for more information.

Research in Canada

Quorum Review IRB maintains an ethics review board (referred to as the "North American" Board) and serves as a duly convened research ethics board (REB) and central institutional review board (IRB). The North American Board complies with Canadian and US requirements and meets twice weekly to review US and Canadian studies. Quorum accepts both privately and publicly funded research.

The submission deadline for the North American Board meeting is one week prior to a scheduled meeting. The North American Board reviews protocol-level materials as well as site submissions that involve research in Canada. Qualifying sites in the US and Canada can be reviewed on a daily basis. Our AAHRPP accreditation applies to review in both countries; we will deliver services according to the same timelines; researchers from either country use the same Quorum Review IRB forms; and with minor differences our submission requirements are the same.

International Research

Each of Quorum Review IRB's Boards may review research conducted outside the United States and Canada. Such research is reviewed in accordance with any applicable United States or Canadian regulations and in accordance with the applicable local laws and regulations of the country in which the research occurs. When reviewing international research, Quorum takes into account the specific local context of the research location. This is accomplished through collaboration with a local Ethics Review Committee or through consultation with Consultant(s) familiar with the research location and its population.

Human Subjects Research Determinations

An applicant may apply to Quorum Review IRB for a determination of whether a proposed activity is human subjects research in accordance with applicable U.S. federal regulations and/or the Canadian Tri-Council Policy Statement: 21 CFR 50.3© and (g); 21 CFR 56.102© and (e); 45 CFR 46.102(d) and (f); TCPS 2, Article 2.1. (Please reference the Human Subjects Determinations Definitions document for specific definitions.) Prior to Quorum Review IRB's review of a Human Subjects Determination Request, the following documentation should be submitted:

- Quorum Review IRB Human Subjects Determination Request Form
- A copy of the final protocol or research proposal (and any supporting material, if applicable)
- Institutional Jurisdiction Waiver Form, if applicable

Please note that as a matter of policy, Regulatory will not make a determination that an activity is not research involving human subjects for FDA-regulated studies. If the sponsor intends to submit the research data to the FDA in support of a research or marketing permit, the FDA regulations apply and such a determination is not applicable. Please contact Quorum Review IRB’s Initial Study Support department with any questions regarding Human Subjects Determinations.

Exempt Research Determinations

Research activities that involve human subjects may be exempt from IRB review under certain conditions pursuant to 45 CFR 46.101(b) (federally funded projects), 21 CFR 56.104(d) (FDA regulated studies), and the Tri-Council Policy Statement 2, Article 2 (Canadian Research). (Please reference Determination of Exemption from IRB Review Checklist.) An applicant may therefore apply to Quorum Review IRB for an exemption determination. Prior to Quorum Review IRB's review of an exemption determination request, the following documentation should be submitted:

- Quorum Review IRB Exemption Determination Request Form
- A copy of the final protocol or research proposal (and any supporting documentation, if applicable)
- Institutional Jurisdiction Waiver Form, if applicable

Board Meetings

Quorum Review IRB has four Boards and conducts up to fifteen convened Board meetings a week. New US protocols can be submitted to five of these meetings (to Board I (Monday and Thursday), Board II (Wednesday and Friday) or Board IV (Tuesday)). To be scheduled to a meeting for review, a submission must be received (with all required elements) by 5:00 p.m. Pacific Time one (1) week prior to the meeting. US amendments can be submitted to one of the daily meetings (Board III) and must be submitted by 5:00 p.m. PT 36 hours prior. Canadian research must be submitted (with all required elements) to either the Wednesday or Friday meetings (Board II) by 5:00 p.m. PT the week prior.

Submission materials scheduled for review are distributed to Board members in advance of the meeting to allow adequate time for the Board members to conduct a thorough review of the materials. Following

Board review, the Board's determination will be communicated to the investigator in writing in accordance with Quorum Review IRB's standard turnaround times (please see the documents "IRB/REB Meeting and Review Cycle Timing" and "IRB/REB Meeting and Review Cycle Timing-Single Site" for turnaround times).

The Initial Review Process

An illustration of Quorum Review IRB's processing and review of a new protocol is available in the Submission Illustration for Central Studies.

The Board considers many factors when reviewing research submissions. For initial review of proposed research, the Board evaluates the protocol and investigational plan to ensure it satisfies specific regulatory criteria, including a favorable risk/benefit ratio, minimization of risks, proper informed consent, and an adequate plan for monitoring data to ensure the safety of participants.

For the review of an investigator, the Board assesses the investigator's qualifications to perform the proposed research, such as medical education, board certifications, prior research experience, and the investigator's experience in the area under study. The Board also reviews information regarding the facility where the research will be conducted and the investigator's plan for conducting the research, including the populations the investigator intends to recruit, the investigator's policies for obtaining the informed consent of participants, as well as the compensation the investigator proposes to provide participants.

An illustration of Quorum Review IRB's process for processing and review of an investigator's submission by the convened Board is available in the Investigator's Initial Submission Illustration.

Quorum Review IRB staff will contact the sponsor or investigator on behalf of the Board should any questions arise in advance of the Board meeting. A prompt response to Quorum Review IRB staff's request will help avoid any delays.

The Possible Outcomes of Board Review

Board review of proposed research or research activities can result in several possible determinations, including:

- Approval: The proposed research or research activity is approved as submitted. Approval documents are issued. Occasionally, the Board may request additional information notwithstanding the approval determination.
- Approval with Modifications: The research or research activity is approved on the condition that Board-requested modifications are incorporated into the research to the Board's satisfaction. The Board will communicate the modifications it deems necessary to approve the research. Examples include submission of additional information regarding a research facility or clarification of a blood draw amount. The modifications must be submitted in writing for review and acceptance by the Board before any approval documents can be issued. A Board decision to approve research with modifications may be appealed by responding with a formal written letter signed by the sponsor or investigator. All appeals must be reviewed at a convened meeting of the Board.

- Approval with Restrictions: The research or research activity is approved, but may only be conducted by the investigator in accordance with Board-imposed constraints, restrictions, or alterations of specified elements. For example, the Board may require the addition of a sub-investigator with a certain expertise or may restrict the enrollment of a proposed recruitment population. Approval with restrictions does not require collection or review of any follow-up material; however, the investigator is required to comply with the Board's constraints. Approval documents are issued.
- Postponement: The Board requires further information in order to make a determination on the proposed research. The Board will communicate the additional information necessary for the Board to make a determination. Once this information is received, the research will be rescheduled according to standard deadlines.
- Disapproval: The Board determines that the proposed research or research activity does not satisfy regulatory criteria for Board approval. The Board will communicate in writing its decision and its rationale for disapproval. A Board decision to disapprove research may be appealed by responding with a formal written letter signed by the sponsor or investigator. All appeals must be reviewed at a convened meeting of the Board.

Following Board Approval

After a study is approved, investigators and sponsors have continuing obligations to:
* Seek prospective Board approval before initiating changes to the approved research;
* Submit recruitment materials and study materials for prospective Board review;
* Promptly report any changes in research activities;
* Promptly report new or updated safety information and potential Unanticipated Problems, including Serious Adverse Events and Major Protocol Deviations/Violations;
* Submit a “Site Status Report for Periodic Review” form in accordance with Quorum's reporting schedule; and
* Submit a “Site Status Report for Closing” form when the study is closed.

As outlined above, proposed research submitted for Board review may result in multiple possible outcomes. After a protocol is approved and proposed consent forms are finalized, the sponsor will receive a Letter of Approval and an electronic copy of the Board-approved consent forms for the study. An investigator will be issued a Notice of Approval if his/her submission is approved, and the sponsor will be copied on the investigator's notification.

Notice of Approval documents are issued following the Board's decision. Included with these approval documents are a copy of Quorum Review IRB's current Board roster and a packet of instructions to help with consenting, study changes, and safety reporting. See the documents “IRB/REB Meeting and Review Cycle Timing” and “IRB/REB Meeting and Review Cycle Timing-Single Site” for the timelines for issuing Notices of Approval.

Expedited Review (EXR)

The Ethics Review Board regulations allow certain types of items to be reviewed by experienced Board members outside of convened Board meetings. The regulations call this process “expedited review” . Quorum Review IRB has expedited reviewers available each business day.

The expedited reviewers can review certain minor changes to previously approved research. Many types of activities, such as participant materials, minor consent form revisions, or administrative protocol amendments can be reviewed through an expedited review process. Additionally, when the Board initially approves or re-approves research “with modifications,” the expedited reviewers usually can make a determination once the requested follow-up information has been received.

Research that is minimal risk and qualifies under one or more of the seven expeditable categories outlined below may reviewed through an expedited review process if requested by the submitting Sponsor. This type of research will be reviewed through an accelerated review process depending on the complexity of the proposal.

Expeditable categories for initial review of research are as follows:

Category 1: Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

Category 2: Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or (b) from other adults and children*, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week

Category 3: Prospective collection of biological specimens for research purposes by noninvasive means.

Category 4: Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing.

Category 5: Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for non-research purposes (such as medical treatment or diagnosis).

Category 6: Collection of data from voice, video, digital, or image recordings made for research purposes

Category 7: Research on individual or group characteristics or behavior

Federal regulations prohibit expedited reviewers from disapproving proposed research activities.

Accordingly, the possible outcomes of EXR include:

- Approval The proposed change is approved as submitted. Approval documents are issued.
- Approval with modifications Modifications to the proposed change are required. The modifications must be submitted in writing for review and acceptance by the Board before any approval documents can be issued.
- Request additional information Further information is required before a determination can be made. Quorum Review IRB staff will follow up with the investigator to request what is needed.
- Refer material for review by the convened Board The proposed change must be reviewed by the full Board. The material will be scheduled for the next available meeting according to standard deadlines.

Translations

Translation Services

If a research participant's primary language is not English, all materials provided to the participant, including consent forms, diaries, questionnaires, and recruitment materials, must be translated into a language understood by the participant. After translation, all materials must be reviewed by the Board prior to its use.

Quorum is dedicated to streamlining the translation of study materials while maintaining appropriate safeguards for participants. The sponsor, CRO, site, or institution has the following options for having translated consent forms and study materials prepared:

- Request that Quorum Review IRB perform the translation; or
- Have the documents translated and send the certified, translated documents to Quorum Review IRB for Board review prior to use.

Further details regarding these options are set forth below. If you have any problems with your translation certifications or any additional questions about Quorum requirements for accepting translation certificates, please contact your Account Manager for help and information.

Translations by Quorum Review IRB

If the sponsor, CRO, site, or institution requests that Quorum Review IRB translate study materials, Quorum Review IRB can arrange for translation into most languages and dialects. Quorum Review IRB has an in-house translations department and also oversees contracted translation vendors as needed to ensure that quality translations are provided to the customer. All translations performed by Quorum Review IRB are certified. Please contact Quorum Review IRB if you have questions or if you would like an estimate of charges or turn-around times.

For the initial translation of a consent form, Quorum Review IRB's **“standard model”** is to start the translation after the English version has been reviewed, approved, and finalized. The time to complete a translation will depend on the document size and complexity; however we are committed to working with

the customer to meet your specific study needs.

Quorum also offers an alternative **“fast track model”** for the translation of initial consent forms. Under this option, the customer can choose to have consent forms translated on an expedited basis so they are completed 72 hours after the English language consent form is finalized. This model produces a fully certified translation. Premium fees apply for the fast track service. The fast track option is available only for the initial translation of a consent form and only if requested during the study submission process.

Translations by Outside Parties

If the sponsor, CRO, site, or institution provides Quorum Review IRB study materials that have been translated by another party, the sponsor, CRO, site, or institution is required to provide a certification of accuracy from the translator.

Quorum generally accepts valid translation certificates, including those from professional translation companies and in-house translation teams employed by a sponsor, Contract Research Organization, site, or institution. In addition, Quorum generally accepts translation certificates from an individual employed by a sponsor, CRO, site, or institution who is fluent in English and the source language, provided that the employee’s primary responsibility involves the translation of study related documents.

Please note that Quorum Review reserves the right to require a back translation or a translation comparison of any translated material submitted to verify the accuracy of the translation. These options are explained below.

- **Translation Comparison**: For a “translation comparison,” Quorum Review IRB reviews and proofreads the translated documents and compares them to the original, Quorum Review IRB-approved English version. If the translation is acceptable, Quorum Review IRB issues a certification of proofreading. A comparison and certification can be completed much more quickly than a traditional back-translation.
- **Back-Translation**: For a “back-translation,” Quorum Review IRB completes a re-translation of the non-English document back into English and then compares it to the original Quorum Review IRB-approved English version. If the translation is acceptable, Quorum Review IRB issues a certification of back-translation. A back-translation can be expensive and time-consuming, but is often required by many sponsors.

Elements of Translation Certifications

Quorum Review IRB generally requires any translation certificate from an outside party to contain the following elements:

- The name and contact information of the company employing the translator.
- The name of the document, including version and/or date if applicable, or other document identifier.
- The source and target language combination (for example, English into Portuguese).
- A statement of attestation that includes the following language (or very similar): “I hereby certify that the identified translated document is, to the best of my knowledge and belief, a true and accurate translation for the original source document.”

- The printed name, title and signature of the person certifying the translation.
- The date of certification.

Canadian French Material

Submission of Canadian French material for studies conducted at Canadian sites may be accepted with a translation certificate as detailed above, or with an attestation from the sponsor, CRO, site, or institution that the Canadian French document is an accurate representation of the English document. The attestation should state that the material was prepared by a business or employee of the sponsor, CRO, site, or institution who normally conducts business in Canadian French and English, and whose primary responsibility involves the creation, editing and/or translation of study-related material.

State and Provincial Law

State and Provincial Laws

In addition to complying with applicable federal regulations regarding the protection of human research participants and investigational drug and device studies, investigators must also comply with state, provincial, or local laws (collectively, “local laws”) that are applicable to the conduct of clinical research.

Among the myriad of local laws an investigator should be aware of are those pertaining to:
* Informed consent;
* Age of consent for procedures involved in research;
* Who may serve as a legally authorized representative;
* Genetic testing;
* Privacy of health information;
* HIV/STD testing;
* Additional protections for humans involved in research; and
* Conflict of interest.

Quorum Review IRB makes every effort to assist investigators in complying with local laws by offering consent form language that complies with applicable laws and regulations. Nevertheless, investigators must rely on their own legal counsel for interpretation of local laws, as it is beyond the scope and charge of an Ethics Review Board to provide such counsel.

Pursuant to federal regulations, sponsors maintain an obligation to monitor the investigators conducting the protocol. Accordingly, sponsors also might offer assistance to investigators regarding local law requirements.

Local Laws and the Consent Form

In addition to federal requirements relating to informed consent, additional requirements may be

imposed upon the written informed consent by local laws. Quorum Review IRB has developed a number of mechanisms for assisting investigators to address local law issues.

First, Quorum Review IRB has generic language to address a number of issues that frequently arise under local law. These issues include the appointment of a legally authorized representative; communicable disease reporting requirements; and notice of mandatory elder or child abuse reporting requirements.

Second, Quorum Review IRB has developed two options for preparing the model consent form to assist investigators in complying with specific local laws: One model consent form If the sponsor chooses this option, Quorum Review IRB will prepare one consent form to be used for all sites. This consent form will incorporate California-specific laws (described below) and other state and local laws. California has the most stringent consent form requirements Quorum is aware of. Two model consent forms If the sponsor chooses this option, two model consent forms will be prepared. Quorum Review IRB will prepare one California-specific form to be used for California sites only. The other consent form, which is designed for use in all states other than California, includes other state-specific requirements. Please note that Quorum Review IRB prepares a model consent form for California because of California's extensive requirements:

- A separate signature line to execute the authorization to release an individual's health information.
- Authorization language in a typeface no smaller than 14-point.
- Language addressing the “recovery time” from the study product or treatment included in the model consent form (“Ask the study doctor for the estimated recovery time of your participation in this study.”)

For more information on California laws, see California Civil Code §56.11(h) and California Health and Safety Code § 24173.

For Canadian research, Quorum Review IRB has developed a model consent form that may be used in all provinces/territories in Canada except those with specific REB registration requirements: Alberta; Newfoundland and Labrador; Quebec when the research involves pediatric participants or participants without capacity to consent; and Saskatchewan.

Finally, Quorum Review IRB encourages investigators to submit any consent form revisions that they believe are required by their particular jurisdictions. For information on how an investigator can submit site-specific consent form revisions, see the section titled “Submitting Unique Consent Forms.”

Age of Majority

Quorum Review IRB is aware of a few states, provinces, and territories where the legal age of majority is over 18, such as Alabama, Nebraska, Puerto Rico, British Columbia, New Brunswick, Nunavut, Nova Scotia, Northwest Territories, and Yukon. For non-pediatric studies Quorum Review IRB will ask the sponsor if they will enroll participants under 21. For these studies where the population between the ages of 18-21 (and the possibility of enrolling those considered minors in some states) will be enrolled, the Board will make a subpart D determination at the time of review.

When sites from the locations listed above submit to Quorum Review IRB, they should indicate that they intend to enroll minor participants when completing the “Site Information Questionnaire.” If the site

indicates they will enroll minor participants that have not reached the age of majority, Quorum Review IRB will automatically create a unique consent form for the site by inserting participant assent lines and other minor working changes.

The HIPAA Privacy Rule

HIPAA Authorizations

The Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA) requires investigators who are “covered entities” to obtain a “HIPAA Authorization” from each participant in a research trial. Obtaining a HIPAA Authorization from a research participant allows the investigator to use and disclose the participant's protected health information (PHI) for research purposes.

As a matter of policy, Quorum Review IRB prefers that all consent forms include language that satisfies the standards of the HIPAA Privacy Rule. Please note that even though Quorum Review IRB reviews HIPAA Authorization language contained within consent forms, it is the investigator's responsibility to comply with the HIPAA Privacy Rule and any applicable state privacy laws. Investigators are encouraged to seek legal counsel to review any HIPAA Authorization language that is used to ensure that it is adequate for the investigator's needs and satisfies state privacy laws.

HIPAA Waivers/Alterations

In some circumstances, it may not be practical for an investigator to obtain an Authorization prior to the use and disclosure of a participant's PHI or to include all the required elements of authorization.

In such circumstances, an investigator or sponsor can apply to Quorum Review IRB for a waiver or alteration of the HIPAA Privacy Rule requirements. Under the Privacy Rule, an Ethics Review Board may approve a waiver or an alteration of the HIPAA Authorization requirement in whole or in part so long as the Ethics Review Board determines that specified criteria are satisfied. The waiver or alteration may be requested at the sponsor level or at the site level. If requested and approved at the sponsor level, researchers and covered entities may rely on the waiver or alteration so long as the documentation is proper. Quorum Review IRB’s documentation of the approval of a waiver or alteration meets regulatory requirements.

There are 3 basic types of waiver or alteration:

- Complete waiver: When the Board grants a complete waiver, the investigator can use and disclose PHI for a particular research trial without obtaining either a verbal or written authorization from the participants. Quorum Review IRB rarely grants complete waivers outside the context of a retrospective chart review or the use of a recruitment database.
- Partial waiver: An investigator may need to record, use, or disclose PHI in the course of a portion of the research without first obtaining a written authorization. This type of waiver is most often requested for recruitment purposes. For example, this can occur when an investigator wants to conduct telephone screens of potential study participants who are responding to an advertising campaign. In appropriate

circumstances, Quorum Review IRB will waive the requirement of a written authorization for this limited portion of the research as long as the investigator obtains verbal permission from the participants and observes certain privacy safeguards.
- Alteration of Authorization: The Board may approve an authorization that has specific required elements of the HIPAA Authorization eliminated. An alteration is most often requested when it is not feasible for the investigator to obtain a signature for the Authorization. This circumstance occurs when the Board has also approved a waiver for documentation of informed consent.

An application form for a complete waiver, partial waiver, or alteration may be obtained by contacting Quorum Review IRB's Initial Study Support Team or by visiting Quorum Review IRB's website.

Recruitment Issues under HIPAA

- Partial waivers for recruitment purposes: As mentioned above, an investigator may need to record, use, or disclose PHI in the course of recruitment without first obtaining a written authorization (i.e., when an investigator wants to conduct telephone screens of potential study participants who are responding to an advertising campaign). Quorum Review IRB encourages investigators to seek partial waivers in conjunction with such recruitment activities.
- Recruitment databases: Some investigators maintain databases with information about individuals interested in participating in research studies. Under federal regulations, the maintenance of a recruitment database is considered a research project separate from individual clinical studies. Investigators who are covered entities must consider the impact of the HIPAA Privacy Rule when collecting PHI for storage in a recruitment database. Investigators might want to obtain written HIPAA authorizations prior to collecting such PHI. Alternatively, investigators might want to apply for a HIPAA waiver to allow the collection of such PHI without a written authorization. Quorum Review IRB asks investigators who seek a HIPAA waiver for purposes of collecting PHI for a recruitment database to submit an application for a complete HIPAA waiver.
- Cold calls: Quorum Review IRB discourages investigators from recruiting participants with “cold calls” based on information derived from the medical records of another practitioner when the investigator has no prior relationship with the recruits. Instead, Quorum Review IRB recognizes the ability of a practitioner to discuss with his or her own patient the possibility of participating in clinical research studies. When a HIPAA waiver/partial waiver is sought for recruitment activities that include “cold calls” for potential recruits, Quorum Review IRB prefers that potential recruits be contacted only by individuals who have been actively involved in providing health care to the potential recruits.
- State confidentiality laws in addition to HIPAA: An investigator must proceed with recruiting carefully in light of the HIPAA Privacy Rule as well as state laws that prohibit the release of medical information without the permission or authorization of the individual.

No Board Review of Additional HIPAA Compliance Documents

Quorum Review IRB understands that the HIPAA Privacy Rule imposes additional requirements on investigators who are covered entities other than those listed above. For example, investigators who are subject to the rule must provide research participants with written notices of their privacy practices, must implement research staff training, and must have in place appropriate administrative, technical, and physical safeguards to protect the privacy and security of PHI. In addition, investigators must comply with state laws that impose more stringent privacy protections than the HIPAA Privacy Rule.

Quorum Review IRB encourages sponsors and investigators to develop a comprehensive HIPAA compliance strategy. Please note however, that aside from HIPAA Authorizations incorporated into consent forms (i.e., compound authorizations) and HIPAA waiver requests, Quorum Review IRB will not review the HIPAA compliance documents developed by an investigator. Quorum Review IRB thus does not review stand-alone HIPAA Authorizations, notices of privacy practices, internal privacy policies, or Standard Operating Procedures as they pertain to HIPAA. Quorum Review IRB will automatically add HIPAA language into the model consent form if it is not included with the consent form. Please contact Initial Study Support regarding this policy if you have any questions.

The Protection of Health Information For Research Conducted in Canada

The federal Personal Information Protection and Electronic Documents Act (S.C. 2000, Ch. 5) (PIPEDA) applies to all organizations in Canada that collect, use, or disclose personal information in the course of commercial activities. PIPEDA states that an organization may collect, use, or disclose personal information only for purposes that a reasonable person would consider are appropriate in the circumstances. If a province or territory in Canada passes a law that is substantially similar to PIPEDA, the organizations or activities covered by the provincial law will be exempted from the federal law for collection, use, or disclosure within the province. For example, Quorum Review IRB is aware that a number of provinces and territories in Canada have specific privacy and data transfer laws. The Board, therefore, expects that the investigator be aware of and comply with all applicable requirements imposed by the federal and local law requirements.

INFORMED CONSENT

Developing the Consent Form

Informed consent is one of the primary ethical and regulatory requirements underpinning research with human participants. Informed consent is an ongoing process that continues through the duration of the study. This section describes Quorum Review IRB's process for the development of an effective written consent form. The following section also sets forth Quorum Review IRB's expectations for the informed consent process.

Consent Forms

When a sponsor submits a protocol for initial review, the sponsor also submits a proposed consent form. When reviewing proposed consent form language, the Board considers whether it:

- Satisfies required elements of applicable regulations and guidelines;
- Accurately reflects the protocol;
- Uses consistent, understandable verbiage;
- Addresses specific Board considerations or requirements; and
- Is consistent with agreed-upon template language with the sponsor (if applicable).

Quorum Review IRB's Sample Language

In an effort to maintain consistency, Quorum Review IRB has developed standardized sample language for many sections of the consent form. This sample language incorporates the Board's preferences and reflects the Board's commitment to using understandable language. Sponsors and investigators who reference Quorum Review IRB's sample language when developing proposed consent forms for a study will generally benefit by having a more expedient review process.

Quorum Review IRB has developed sample language on a variety of topics, including genetics, assent by minors, and photography. Sponsors and investigators can obtain the current version of Quorum Review IRB's sample language by contacting Quorum Review IRB or by downloading the forms from the secure area of Quorum Review IRB's website. Additional information about Quorum Review IRB's consent form preferences are available in the guidance document “Consent Form Development Guide,” which also is available upon request or on Quorum Review IRB's website (www.QuorumReview.com).

Developing and Finalizing a Consent Form

As a part of the regulatory criteria for review of proposed research, Ethics Review Boards are required to ensure that informed consent will be obtained and documented to the extent required by federal

regulations. To that end, the Board may require revisions to a proposed consent form for a study. After the Board has reviewed and revised a consent form, an electronic copy of the Microsoft Word document is returned to the customer by e-mail for review and comment before finalization. Customers are expected and encouraged to submit revisions to the changes made by the Board. All such revisions must be submitted to the Board for review and approval. Please note some sections of a Quorum Review IRB revised consent form will correspond with information reported by investigators in response to specific questions on the Site Information Questionnaire. Examples of such sections involve potential conflict of interest, witness statements for the enrollment of illiterate participants, and the use of legally authorized representatives. These sections reflect Board-required language and are provided for reference but are generally not modifiable. If sponsors have different requirements for the language in these sections than what is proposed by Quorum Review IRB, it is recommended that sponsors negotiate and establish "locked-in" template language to be used in all of their consent forms (see the Client Template Language section below).

Rationale is perhaps the most frequently overlooked submission requirement for consent form revisions. A well-written rationale from the Sponsor or Investigator helps the Board provide an accurate and fair review.

Any changes to consent forms requested by customers must be submitted as tracked-in changes to the Microsoft Word document using the Microsoft Word tracking feature and accompanied by a written rationale for the requested changes. The written rationale may be a document separate from the revised consent form, or it may consist of comments inserted into the revised consent form using the comments feature in Microsoft Word.

Once the Board has approved the proposed consent form language and the customer has accepted the Board's revisions, Quorum Review IRB considers the consent form to be finalized as of the date of the last Board review. As investigators become approved to participate in the study, Quorum Review IRB will provide a stamped, approved copy of the finalized consent form with site specific information (address, telephone numbers, compensation) inserted along with the approval document.

Client Template Language

In order to support consistency in Quorum Review IRB's revisions and make the consent form development process more expedient, Quorum Review IRB offers clients the opportunity to develop "locked-in" template language with Quorum Review IRB. This process allows for Quorum Review IRB and a client to come to agreement on the use of specific language to be used across studies. Clients can choose to develop locked-in language for entire forms or to develop particular sections (such as HIPAA authorizations, conflict of interest, or compensation for study-related injury/illness).

Clients are encouraged to submit proposed template language to the Board for review. Once the Board has approved the language and the client has accepted any revisions made by the Board, the language will be considered "locked" and binding upon both the client and Quorum Review IRB for the upcoming year. After the template language is locked in, Quorum Review IRB will revise the locked-in sections of newly proposed consent forms only as necessary to make the language consistent with the agreed-upon template, as mutually agreed upon in advance or as necessitated by changes in the laws or regulations governing research.

Clients who are interested in developing template language should contact Quorum Review IRB's Client

Relations Team at (206) 448-4082.

Model vs. Unique Consent Forms

When Quorum Review IRB is chosen as the central Ethics Review Board for a study, the consent form is developed in cooperation with the sponsor and is approved by the Board to be used by all investigators who are approved by the Board to conduct the study. This consent form is called the “model consent form.”

Investigators do not need to submit a consent form to Quorum Review IRB if they intend to use the approved model consent form (as indicated by the investigator on the “Site Information Questionnaire”).

Alternatively, an investigator may request changes to the model consent form. Once such revisions are approved, Quorum Review IRB refers to such consent forms as “unique consent forms.”

Examples of modifications requested by investigators include revisions to fulfill state law requirements and revisions to describe site-specific policies.

Submitting Unique Consent Forms

If an investigator decides to submit a unique consent form, the changes must be tracked into an electronic copy of the current Board-approved Microsoft Word version of the model consent form using the Microsoft Word tracking feature and submitted to Quorum Review IRB by e-mail. The investigator also must submit written (or e-mailed) sponsor approval of the proposed unique consent form change as well as rationale for all requested changes. Additionally, if the sponsor has elected to not pay for unique consent forms, the site will be responsible for payment.

Requirements for unique consent form submission:
* Electronic version of the currently approved Quorum Review IRB model consent form tracked with the investigator's unique changes.
* E-mail or fax indicating Sponsor approval for the unique language.
* Rationale for the investigator's unique changes (e.g., to comply with local laws).

Unique consent forms that are not submitted with all required elements (noted above) will not be scheduled for review until all required elements are received. Quorum Review IRB staff will notify the investigator of any missing elements if a proposed unique consent form does not meet Quorum Review IRB's requirements.

Privacy/Confidentiality

Federal regulations mandate that consent forms address privacy and confidentiality issues including the extent to which records identifying participants will be kept confidential. Additionally, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) imposes heightened obligations on covered entities in obtaining written authorizations for the use and disclosure of personal health information. In order to assist investigators and in light of HIPAA's articulation of privacy interests, Quorum Review IRB

prefers that all consent forms approved by the Board address privacy and confidentiality issues to the extent required by the HIPAA Privacy rule as well as by federal regulations for the protection of human research participants.

For more information on Quorum Review IRB's policies involving HIPAA, see the section titled "The HIPAA Privacy Rule."

Compensation and Reimbursement

When a sponsor chooses Quorum Review IRB as the central Ethics Review Board for a study, Quorum Review IRB recognizes that each investigator may choose to compensate and/or reimburse participants differently. As a general rule, all compensation/reimbursement given to participants during the study must be described in the consent form. "Compensation" refers to payment for participation in a research study. "Reimbursement" includes reimbursement for parking and travel, the provision of gifts for participant retention purposes, or the provision of medical devices to be retained by the participant following the study, etc.

Generally, payment arrangements may not make more than 40% of the total compensation amount contingent upon completion of the study.

Upon Board approval of the investigator's "Site Information Questionnaire," Quorum Review IRB staff will incorporate the investigator's compensation plan into the investigator's Board-approved consent form.

Sponsors may choose to require all investigators to provide the same compensation amounts or restrict investigators from providing compensation to participants. In this case, the sponsor should inform investigators of the required compensation plan and the information from the investigator's SIQ should match the compensation amounts listed in the model consent form. Informing the investigators ahead of time will help avoid delays. If an investigator wishes to deviate from the sponsor's required compensation plan, the investigator should request a "unique consent form" by marking the appropriate box on the SIQ and following the requirements for submitting a unique consent form (listed above in the section titled "Submitting Unique Consent Forms").

Conflicts of Interest

Quorum Review IRB strives to follow the federal and clinical research industry standards for managing and minimizing potential conflicts of interest held by study staff and their immediate family members. The Board expects an investigator to disclose any individual financial interests held by the investigator, a research staff member, or an immediate family member (spouse, domestic partner, and dependent children) with respect to any company that may benefit from the proposed research activity. The Board may elect to have the potential conflict of interest disclosed to potential participants via the consent form document. For more information regarding conflict of interest, please see the section titled "Conflict of Interest" in Chapter 2.

Electronic Informed Consent

Electronic informed consent is generally defined as a digital representation of what would otherwise be presented to prospective subjects in a hard-copy consent form. It may be accessed on various electronic devices and through software, a website, or other applications. Electronic informed consent may include audio, video, animation, or other multimedia content that would not be included in the hard-copy consent form.

For information on Quorum's process for reviewing electronic informed consent submissions, see our client guidance document, "Electronic Informed Consent at Quorum Review,." on Quorum Review IRB's website.

Services for Developing and Revising Consent Forms

Quorum Review IRB is happy to develop or revise consent forms on behalf of clients.

Custom Consent Form Creation Service

To develop new consent forms, Quorum Review IRB offers a Custom Consent Form Creation Service that draws on the combined expertise of our regulatory and consent form development staff, who will collaborate to produce custom consent documents for your study. This eliminates the requirement that the client provide consent documents as part of its initial study submission.

In general, documents produced through the Custom Consent Form Service will be based on Quorum Review IRB consent form templates, which have been designed to accommodate a wide variety of research studies and include element required by regulation, established industry guidelines, and state laws. In addition, upon request the documents produced will incorporate any relevant client template language that may have been created by Quorum Review IRB and the Sponsor, CRO, Site or Institution.

Consent Form Revision Service

If you have existing, approved consent forms that require modification, Quorum Review IRB offers a Consent Form Revision Service to assist with the preparation of the revised document. With this service Quorum Review IRB staff will make the revisions to the consent form(s) on the client's behalf.

Please contact Quorum Review IRB if you would like additional details on these services or if you would like an estimate of charges or turn-around times.

Consent Form Versioning

Model Consent Form

The version number issued for a Quorum approved model consent form is always a whole number (i.e. Version 1, Version 2, etc.). The initial model consent form approved by the Board is numbered "1" and

dated the date of the last Board Review. Version 2 and greater are issued when the Sponsor/CRO or IRB request a template change due to updated information (i.e. amendment to the protocol, updated safety information, etc.).

Consent forms in draft form (i.e. the consent form template submitted by the Sponsor/CRO with the initial submission), will begin at Version 0. Any modification to a draft consent form will result in an increase of a "point" throughout the consent form finalization process (i.e. Version 0.3, Version 0.4, etc.).

Central Site Consent Forms

The version number for a central study investigator's consent form may be either a whole number, a "point" version (Version 1.1, Version 1.2, etc.), or an "alpha-numeric" version (Version 1a, Version 1.1a, Version 1b, etc.).

If the only modifications to the initial model consent form is the inclusion of site-specific information (i.e. the Investigator name, address(es), emergency contact information, and compensation information), the consent form issued to the investigator after approval will have the same version number and date as the model consent form. The majority of investigators will receive these whole number versions with their initial approval documents unless a "unique" consent form request has been submitted.

Unique consent forms are requests to modify the model consent form in some manner beyond the insertion of site-specific information in the placeholders. Unique consent forms are issued using "point" versioning (i.e. Version 1.1, Version 2.1, etc.). The date of the pointed consent form is the date of the Board's approval of the investigator's modifications. Additionally, pointed consent forms are issued for investigators that request to use the optional (highlighted) consent form language. This optional language includes witness statements, language for use of a legally authorized representative, or language for potential conflicts of interest. These investigators will always be issued a pointed consent form during version updates to the model consent form (i.e. Version 2.1, Version 3.1, etc.). This pointing system is used to alert Quorum staff that this investigator has approved additional language or modifications that should be incorporated into future revised model consent forms.

A pointed consent form is also issued if an investigator requests a site-specific revision to their current consent form during the course of the study (for example, to reflect a change in address or phone number). The consent form number increases by .1 (i.e. Version 1.1, Version 1.2, etc.) and the consent form is dated the date that the Board approves the revision. This pointing system is used in these instances to keep the investigator on the same version number as the model consent form. If a revised model consent form is approved at a later date, and the investigator is not unique, Quorum will issue that investigator a whole number version (not pointed).

An "alpha-numeric" consent form is issued to an investigator to correct an error made in a previously issued consent form (for example, the address or telephone number was incorrect). The corrected consent form version increases by a lower case letter beginning with the letter "a" (i.e. Version 1a, Version 1.1a, Version 2b, etc.). The date of the alpha-numeric consent form is the same date of the previously issued form which contained the error.

Single Site Consent Forms

The version number for an approved consent form on a single site study may be either a whole number

(i.e. Version 1, Version 2, etc.) or an “alpha-numeric” version (Version 1a, Version 2a, Version 3b, etc.).

The version number issued for a single site Quorum approved consent form is regularly a whole number (i.e. Version 1, Version 2, Version 3, etc.). The initial consent form approved by the Board is numbered “1” and dated the date of the last Board Review before finalization. Version 2 and greater is issued when the investigator submits a change due to updated information (i.e. amendment to the protocol, updated safety information, etc.) or the investigator requests a site-specific change to their facility (i.e. to reflect a change in address or phone number).

Single site consent forms in draft form will begin at Version 0. Any modification to a draft consent form will result in an increase of a “point” throughout the consent form finalization process (i.e. Version 0.3, Version 0.4, etc.).

An “alpha-numeric” consent form is issued to a single site investigator to correct an error made in a previously issued consent form (for example, the address or telephone number was incorrect). The corrected consent form increases by a lower case letter beginning with the letter “a” (i.e. Version 1a, Version 2a, Version 1b, etc.). The date of the alpha-numeric consent form is the same date of the previously issued form which contained the error.

Translated Consent Forms

Translated consent forms that are issued by Quorum will have the same version number and date as the previously-issued English Version.

Informed Consent Process

Informed Consent Discussion and Monitoring, and Documentation of Informed Consent

The Board allows investigators to personally conduct informed consent or to delegate the task to a qualified staff member. When conducting the initial informed consent discussion, the investigator must ensure that the participant or their legally authorized representative (LAR) has adequate time to read the consent form and has questions answered. The investigator shall also ensure that the person administering the discussion and the participant or their LAR sign and date the consent form at the time of the informed consent discussion. The participant or their LAR (whoever signs the consent form) must receive a copy of the signed form at the time of consent.

While federal regulations do not require the Board to monitor the consent form process on a routine basis, situations may arise where the Board finds it appropriate to monitor the informed consent process. Some examples include research involving vulnerable populations or unfavorable review from the FDA, sponsor, or other relevant agency. The Board may make requests such as additional documentation, copies of the signed consent form, witness signatures, or a site visit as a means of monitoring the informed consent process.

The investigator must retain signed consent forms consistent with federal regulations and any other applicable laws, and be able to produce the forms to Quorum Review IRB upon request.

An illustration of initial and ongoing informed consent is available in the Informed Consent Illustration: Initial and Ongoing.

When conducting the informed consent discussion, the investigator must use the most appropriate recent Board-approved version of the consent form. Included with this responsibility is the provision of a Quorum Review IRB-approved consent form in the participant's primary language to all non-English-speaking research participants (see the section titled "Non-English-Speaking Participants" below).

Children, Minors, and Assenting Requirements

For studies involving minor participants, Quorum Review IRB requires written informed assent of minors ages seven and older. Additionally, as required by federal regulations, when the Board approves research involving minors, the Board must determine whether the written permission of one or both parents of a minor is required, based on the expected level of risk and prospect of benefit to the minor participants involved in the research. The Board may require both parents to provide written permission in addition to the minor giving his or her informed assent. However, if one parent is not reasonably available (deceased, unknown, or legally incompetent) or if only one parent has legal responsibility for the care and custody of the child, it is acceptable for only one parent to give permission even when the Board has required the permission of both parents.

As a general rule, when Quorum Review IRB approves a study involving minors, Quorum Review IRB will prepare a consent form that includes a parental permission signature line. If the investigator seeks to have the parental signature line removed because the investigator intends to enroll an emancipated or mature minor, the investigator will be asked to submit a letter of explanation. The letter should address:

- The local laws by which the investigator believes the minor(s) can provide legally effective consent to be enrolled in a research study without parental permission; and
- The safeguards the investigator plans in order to protect such minors, including how the investigator will confirm that such potential participants understand the difference between "research" and "treatment" and, if appropriate, the import of consenting to research that involves a placebo arm.

Legally Authorized Representatives

A legally authorized representative (LAR) is defined by 21 CFR § 50.3 as, ". . . an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research." A properly qualified LAR may make decisions on behalf of and for the participant, but the specifics of how to qualify an LAR are defined in local laws. It is the investigator's responsibility to ensure compliance with his or her local laws that govern LARs and to have a system in place to ensure that only properly qualified LARs consent to research decisions for a participant. For more information on the use of an LAR, please see the "Legally Authorized Representative" guidance document.

If the investigator anticipates the possibility of using an LAR when filling out initial submission materials, the investigator should indicate accordingly on the "Site Information Questionnaire." Additionally, if the protocol affirmatively states that LARs are allowed, please indicate accordingly on the "Central Study

Questionnaire."

The Board will determine whether the use of an LAR is appropriate under the protocol and whether the investigator's site appears qualified to enroll subjects that may require the use of an LAR.

Quorum Review IRB expects investigators to obtain continuing assent from adult participants who lack the decisional capacity to consent to research. Even if an LAR has authorized an individual's participation, an investigator has an obligation to discontinue that individual's participation should the individual express fear, discomfort, or any disagreement with study procedures.

Adult Participants with Diminished Decision-Making Capacity

The Board recognizes that adults with decisional impairments may be vulnerable to coercion and undue influence. While the impairment may fluctuate or progressively deteriorate over time, the Board considers capacity in relation to the specific task or decision-making circumstance.

Generally, the Board does not agree to involve incapable participants in research that could be conducted with capable participants. The exception to the general rule is if the research provides access to an important potential benefit, particularly a benefit that is not otherwise available to the participant.

When the Board reviews research involving adults with decisional impairments, it may require a variety of safeguards such as capacity assessment tools and proxy consent.

Participants Who Are Unable to Read

When the Board approves research, it also makes a determination whether or not it is appropriate to enroll participants who cannot read or write. This decision is based on protocol requirements such as individual completion of required diaries, medication logs, and/or questionnaires.

If an investigator wishes to enroll participants who are unable to read, upon review and approval of the process for consenting participants who are unable to read, the investigator will be issued a consent form that includes a witness statement and signature lines to be completed by an impartial witness on behalf of the participants who are unable to read. The impartial witness will attest to the completeness of the informed consent discussion and the participant's voluntary agreement to participate in the study. The investigator or members of the study staff are not considered impartial witnesses.

Non-English-Speaking Participants (Subjects with Limited English Language Proficiency)

As required by federal regulations, the consent form must be written in language understandable to the participant (or his/her legally authorized representative). When the informed consent discussion is conducted in English, the consent form should be in English. When non-English-speaking participants are recruited for research, Quorum Review IRB requires that a Board-approved translated consent form be provided to non-English-speaking participants in their primary language during the initial informed consent discussion.

Investigators must indicate their intent to enroll non-English-speaking participants during initial submission by completing the appropriate section of the “Site Information Questionnaire” form. If the Board approves the enrollment of non-English-speaking participants, the investigator must ensure that a research staff member or other interpreter (other than a family member) who is fluent in the relevant language is available for both the initial informed consent discussion and throughout the duration of the study in order to explain study visit processes and procedures, to explain any changes to the research, to provide new information, to answer any ongoing questions, and in case of an emergency.

Please see the above section titled “Translations” for more information regarding how to request a translated consent form.

Consent Form Waivers

Waiver of Documentation of Informed Consent

Consistent with applicable regulations and guidelines in the US and Canada, the Board has the authority to approve a request for a waiver of documentation of informed consent provided that certain criteria have been established. Prior to the Board's review of a new study submission, the sponsor or site should complete and return the “Waiver of Documentation of Informed Consent Submission” form in addition to the other required submission documents. Please note that the Board will grant such a request only if the sponsor or site can demonstrate that a complete and adequate consent process will take place even though the requirement for documentation of that process is waived.

To demonstrate that an adequate consent process is occurring, a copy of the information sheet provided to participants or their LAR is required as part of the initial study submission. Depending on your study, the information sheet could be a consenting script that is read to participants over the phone, an online consent document that participant logs in to read, and/or a written document given to participants by study staff. The information sheet should include the required elements of informed consent with the exception of documentation (signatures), unless you have also requested an alteration of one or more of the required elements of consent.

Waiver or Alteration of Informed Consent

For non-FDA research regulated by the HHS regulations and for research in Canada, the Board has the authority to waive or alter the requirement to obtain informed consent from research participants provided that certain elements are satisfied. In a situation where an applicant seeks a waiver or alteration of informed consent that applies to more than one research site, the Board may grant the request for a waiver or alternation of consent for any and/or all sites, if appropriate. For FDA-regulated studies, the Board will not grant a request for a waiver or alteration of informed consent.

Prior to the Board's review of a new study submission, the sponsor should complete the “Waiver or Alteration of Informed Consent Submission” form in addition to the other required submission documents.

STUDY START-UP

Research Submissions

All submission forms submitted to the Board must be completed in their entirety. Failure to sign or complete submission forms will result in a delay in scheduling submission materials for Board review.
Quorum Review IRB staff will contact the sponsor or investigator to request any missing information.
Quorum Review IRB does not advise scheduling participants until approval documents are issued.
Research may not commence until Quorum Review IRB has issued all required approvals.

Quorum Review IRB is committed to working with investigators and sponsors to make the study start-up process as straightforward and efficient as possible. As part of this effort, all required Quorum Review IRB submission forms and guidance are available on the Quorum Review IRB website at www.QuorumReview.com.

All submission documents can be faxed, mailed, or submitted electronically to Quorum Review IRB. Please check Quorum Review IRB's website or contact Quorum Review IRB with questions about the submissions process. Quorum Review IRB's Client Support Team is available to aid investigators in the submission process at (206) 448-4082.

Central Studies

Quorum defines a central study as a study in which the sponsor or sponsor representative has designated Quorum as the central IRB for the study. Protocol level decisions are made by the sponsor or sponsor representative on behalf of site(s). When Quorum Review IRB is identified as the central Ethics Review Board for a study, the sponsor must submit the following documents to Quorum Review IRB on behalf of investigators:

Helpful Hints Submitting the Protocol
Please see the guidelines in "Protocol Contents" document for assistance in drafting a protocol that contains all the elements the Board is looking for.

- Study protocol (see "Protocol Contents" guidance document)
- All proposed consent forms (in electronic Microsoft Word format)
- Investigator's brochures, package inserts, or device background literature for all primary and comparator drugs/devices
- "Central Study Questionnaire" form
- "Device Study Submission" form (as applicable)
- Proposed study-wide advertisements and recruitment materials
- Proposed study-wide participant materials (diaries, questionnaires, written study instructions, etc.)

Helpful Hints Submitting Investigator Materials
Please see the guidelines in the Site Information Questionnaire Workbook for assistance in preparing investigator submission materials.

The following items must be submitted by the investigator:

- "Site Information Questionnaire: Primary Research Facility" form
- Principal investigator's curriculum vitae including research experience and education
- Sites conducting research in any jurisdiction which does not provide online license verification (e.g. Puerto Rico, certain Canadian provinces, etc.): Hard copy of Principal investigator's medical license

Depending on the site and study, some supplemental material may be necessary as part of the site submission, such as:

- "Additional Research Facility Site Information Questionnaire" form
- Proposed site-specific advertisements and recruitment materials. These materials should be accompanied by written sponsor approval if this is required by the sponsor
- Proposed site-specific participant materials (diaries, questionnaires, written study instructions, etc.)
- Supplemental material as appropriate based on "Site Information Questionnaire" responses (for example, FDA audit information, letters of explanation, etc.)

Single Site Studies

Quorum defines a study as a single site when the sponsor has not identified Quorum Review IRB as the central Ethics Review Board for the study and the investigator has elected to submit the study for review. The investigator is the Quorum contact for all site and protocol related decisions. The following items must be included in the submission for single sites, in addition to the investigator submission items listed on the previous page:

- Study protocol (see "Protocol Contents" guidance document)
- All proposed consent forms (in electronic Microsoft Word format)
- Investigator's brochures, package inserts, or device background literature for all primary and comparator drugs/devices
- "Single Site Study Questionnaire" form
- "Device Study Submission" form (as applicable)
- Proposed site-specific advertisements and recruitment materials
- Proposed participant non-recruitment materials (diaries, questionnaires, written study instructions, etc.)

Investigator-Generated Protocols

Quorum Review IRB reviews research initiated and conducted by individual investigators. Generally, in these types of studies, the principal investigator is acting as both the sponsor and the investigator (a "sponsor-investigator" under FDA Regulations). The following items must be submitted:

- Study protocol (see "Protocol Contents" guidance document)

- All consent forms (in electronic Microsoft Word format)
- Investigator's brochures, package inserts, or device background literature for all primary and comparator drugs/devices
- "Device Study Submission" form (as applicable)
- Proposed site-specific advertisements and recruitment materials
- Proposed participant non-recruitment materials (diaries, questionnaires, written study instructions, etc.)
- "Single Site Study Questionnaire" form
- Proof of liability coverage for the principal investigator conducting the study
- Indemnification Agreement with Quorum Review IRB by the principal investigator
- Institutional Jurisdiction Waiver (if applicable)
- Institutional Authorization Agreement (IAA) (if applicable)

Depending upon the nature of the study, investigator-generated protocols may have further submission requirements not outlined above. For more information, please contact Quorum Review IRB's Initial Study Support Team at (206) 448-4082.

Retrospective Chart Review Submissions for Single Sites

Quorum Review offers streamlined processing for single-site retrospective chart review protocols. In general, you can use this simplified process if both of the following are true:

- You plan to conduct the retrospective chart review with a complete consent waiver.
- You also plan to seek Board review of the research as a single-site study, where Quorum does not act as a central review Board—instead, Quorum communicates directly and exclusively with the primary investigator's (PI's) site, and the site is responsible for providing Quorum with all study material.

If the above criteria are met, Quorum's simplified submission requirements are as follows:

- Study protocol (see "Protocol Contents" guidance document)
- "Questionnaire for Single Site Research: Retrospective Chart Review" form
- "Expedited Review Request for Initial Review of Research" form
- Study and/or data collection tools (if applicable)

Co-Principal Investigator Submissions

Co-principal investigators are generally not permitted by the Board, as the Board recognizes identification of one principal investigator as the preferred means of ensuring a single point of responsibility and authority. In individual cases, the Board may find identification of more than one principal investigator acceptable. In such cases, the Board requires a letter from the co-principal investigators indicating the rationale for the co-principal investigator arrangement and identifying one of the principal investigators as the primary contact for matters related to Board oversight. All required documents must also be signed by both principal investigators.

IRB Jurisdiction

Quorum Review IRB has a standard process by which an institution's IRB may waive jurisdiction of a particular study to Quorum Review IRB. This waiver should be included with the initial site submission. In some cases, an institution may require that both parties sign a formal agreement. This agreement often is known as an Institutional Authorization Agreement (IAA), and can be issued either on a site-specific basis or as a master agreement between Quorum Review IRB and the institution. Please see the SIQ Workbook for guidance on submitting a waiver of jurisdiction or IAA as part of a site submission. Please contact Client Relations regarding a Master IAA with Quorum Review IRB.

Federally Funded Studies

Submission Requirements

Prior to the Board's review of federally funded research, the following documentation must be submitted in addition to other required material for review of new protocol submissions:

- A completed Federal Funding Addendum (available on our website or from Initial Study Support).
- A complete copy of the applicable grant application or other funding application. (The grant application or other funding applications typically does not need to be reviewed by Quorum Review IRB for a non-awardee institution involved in a multi-site research project. Please contact Initial Study Support if you have questions about a multi-site research project.)
- A copy of the federal contract (if available).
- A valid Federal Wide Assurance (FWA) number. A Federal Wide Assurance (FWA) must be filed for each legal entity engaged in the federally funded study as required by 45 CFR § 46.103 and in accordance with the following OHRP guidance: ("Engagement of Institutions in Research"). A copy of the FWA form may be downloaded from the following OHRP website: http://www.hhs.gov/ohrp/assurances/. (Please contact the applicable agency if using a different assurance process other than a FWA.)
- A completed IRB Authorization Agreement (IAA). (Quorum Review IRB will accept any standard IAA form. You may obtain Quorum's template IAA from our website (www.QuorumReview.com).

Federal Wide Assurance Requirement for IRBs

An independent IRB does not need to obtain a separate FWA. It is generally accepted that the IRB is not actively engaged in the research nor is it a direct recipient of federal funds. Consequently, the IRB can be considered a sub-contractor and as such should be listed on the sponsor's FWA form as the IRB of record. More information is available at http://www.hhs.gov/ohrp/policy/expedited98.html.

Please contact Quorum Review IRB's Initial Study Support Team for clarification or assistance regarding these requirements.

Submission Timelines

Complete submissions received by 5:00 p.m. PT will be scheduled for the Board meeting five (5) business days later.
Please note: Holidays can affect the meeting schedule of the Board and the above deadlines associated with submissions. You can find the current Board meeting schedule online at www.QuorumReview.com.

To allow adequate time for Board preparation and review, Quorum Review IRB requires that all submission materials are received by 5:00 p.m. Pacific Time (PT) at least one week in advance of the Board meeting at which they will be reviewed. Board meetings are held each day of the workweek, excluding major holidays. Quorum Review IRB will assess sites on a daily basis and some sites will receive a decision on an accelerated schedule.

Quorum Review IRB recognizes rapid study start-up is essential to running a successful study, and is dedicated to helping customers meet their goals. Informing Quorum Review IRB of your anticipated timelines for study start-up can help Quorum Review IRB better serve you.

Quorum Review IRB strongly advises against scheduling site initiation visits, participant screening, or any other study activities until you have received Board approval. Unforeseen and unavoidable delays in review may occur during your study start-up.

IMPORTANT NOTE: Incomplete submissions are not scheduled for Board review. Submission materials that are missing required elements or that require additional clarification are not scheduled for Board review until the forms are complete and the issues resolved. Quorum Review IRB staff will contact the investigator the day we receive the submission and then at least once weekly to request missing elements. Once the missing information or documentation is received, the submission will be scheduled for the next available Board meeting in accordance with the submission timelines above.

IMPORTANT NOTE: Research may not commence until Quorum Review IRB has issued all required approvals. Additionally, please note that if the research requires additional non-IRB approvals, such as Institutional Biosafety Committee (IBC) approval, research may not commence until after such approval is received.

Site Submission Status Report

When Quorum Review IRB serves as the central Ethics Review Board for a multi-site study, a site submission status report is available on Quorum Review IRB's OnQ Portal and is updated throughout the day to keep the sponsor study contact informed of the status of investigators' submissions. This update provides the following information for each investigator that has submitted to be part of the study:

If you are a Sponsor and do not already have access to Quorum Review IRB's OnQ Portal, please contact Quorum Review IRB's Initial Study Support Team to learn more about this service or to obtain a password.

1. Site Status: Shows if the site is being held for missing information, scheduled for review, or is Approved/Active in Quorum Review IRB's system.
2. Initial Review Date: Shows which investigators' submissions have been reviewed and the date of initial review.
3. Approval Ship Date: Shows the date on which Notice of Approval documents were shipped to the

investigator.
4. Submission Follow-up Activities: Shows which investigators have submitted incomplete documents and the weekly calls, e-mails, or faxes that Quorum Review IRB staff made to obtain the missing information so the submissions can be scheduled for Board review.

Emergency Use of an Investigational Test Article

Quorum Review IRB typically does not review planned emergency research. Quorum Review IRB acknowledges, however, that at times an investigator will be presented with a situation in which a study has not yet been approved by the Board but a participant unexpectedly presents himself/herself in an emergent situation. The use of an investigational test article (for example, drug, device, or biological product) prior to Board approval is inappropriate. Under exceptional circumstances, however, federal regulations exempt emergency use of an investigational test article from Board review and approval when, in the investigator's judgment:

1. The participant presents with a life-threatening or severely debilitating condition;
2. No standard acceptable treatment is available; and
3. There is not sufficient time to obtain Ethics Review Board approval.

When an investigator determines emergency use of an investigational test article is necessary and meets the requirements exempting it from the prior Board review requirement, the investigator should notify Quorum Review IRB promptly by phone before the test article is administered. Thereafter, the investigator must report the details of the emergency use to the Board (for example, description of the life-threatening situation, why standard acceptable treatment was unavailable, and why there was not sufficient time to obtain prospective Board approval) within five (5) business days of the emergency use.

> “Life-threatening” means diseases or conditions with potentially fatal outcomes or where the likelihood of death is high unless the course of the disease or condition is interrupted. Life-threatening also includes diseases or conditions that cause major irreversible morbidity such as blindness, loss of a limb, paralysis, or stroke.

The investigator must obtain informed consent from the participant or his/her LAR before administering emergency use of a test article unless both the investigator and a physician not participating in the research certify in writing that:

1. The participant is confronted by a life-threatening situation necessitating the use of the test article;
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent, from the person;
3. Time is not sufficient to obtain consent from the participant's LAR; and
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the participant's life.

If, in the investigator's judgment, use of the test article is required to preserve life, and time is not sufficient to obtain the independent determination of the above informed consent certification, the investigator should make the required determination, secure in writing the independent physician's review and evaluation, and submit the documentation to Quorum Review IRB within five (5) business days of the emergency use.

PARTICIPANT MATERIAL AND RETENTION PROGRAMS

Quorum Review IRB considers recruiting activities to be the beginning of the informed consent process. Consequently, in accordance with its authority to approve or disapprove all research activities, the Board requires prospective review of all recruitment materials that are intended to be seen or heard by prospective participants to solicit their participation in a study. Likewise, protocol study tools, study materials and participant retention programs intended to encourage enrolled participants to continue participation in a study or provide participants with study-related information must be reviewed and approved by the Board before implementation.

When submitting participant materials or retention programs, please refer to the Participant Material and Retention Program Submission Cover Page at www.QuorumReview.com.

Please see the "Participant Material and Retention Program Guidelines" for details.

For additional information about recruiting activities such as recruitment databases, telephone scripts and cold calls see the section "Recruitment Issues under HIPAA" in Chapter 2. For additional information about enrollment bonuses and finders' fees, see the section "Conflict of Interest" in Chapter 2.

SAFETY REPORTING

Prompt Reporting Requirements for Safety Information and Unanticipated Problems

Prompt Reporting Requirements

Pursuant to federal regulations, Ethics Review Boards are required to follow written procedures to ensure that investigators promptly report “Unanticipated Problems Involving Risk to Participants or Others” to the Board, appropriate institutional officials, and appropriate regulatory authorities. Accordingly, Quorum Review IRB adheres to procedures that require investigators to promptly report certain events within ten (10) business days of becoming aware of the event's occurrence. These “Reportable Events” include:

- Serious Adverse Events
- Major Protocol Deviations/Violations
- Research participant complaints
- Adverse audit or enforcement actions (e.g., Form FDA 483, FDA Warning Letters, FDA Establishment Inspection Reports (EIRs), adverse sponsor audit findings, etc.)
- IND Safety Reports that qualify as Unanticipated Problems
- New/updated safety information that may increase risk to participants
- Reports, publications, or interim results or findings
- Recalls, withdrawals, or clinical holds
- Any other incident that could qualify as an Unanticipated Problem
- Any incident that must be reported according to the policies of the sponsor or site

For additional guidelines regarding the types of incidents that require prompt reporting, refer to the Safety Information and Unanticipated Problems Reporting Guidelines (“Safety Reporting Guidelines”) located on Quorum Review IRB's website. The Safety Reporting Guidelines include a one-page summary with examples that can be posted in a convenient place at the research facility.

Reportable Events and Board Review

When a Reportable Event is submitted to Quorum Review IRB, Quorum Review IRB staff conducts a preliminary analysis as to whether the event meets Quorum Review IRB's safety reporting requirements. Reportable Events that satisfy Quorum Review IRB's reporting criteria are then evaluated by Quorum Review IRB's Medical Consultant – an experienced physician Board Member. The Medical Consultant may determine that a particular Reportable Event should be evaluated at a convened Board meeting for a determination as to what, if any, action is appropriate and whether the event qualifies as an “unanticipated problem involving risk to participants or others.” If the Board determines that the event qualifies as an unanticipated problem involving risk to participants or others, Quorum Review IRB is obligated to report the event to the sponsor, appropriate institutional officials, and the FDA. Even if an

incident does not qualify as an unanticipated problem, the Board may take further action to ensure the safety and welfare of research participants.

Serious Adverse Events

Helpful Hints Reporting Adverse Events and Protocol Deviations
To determine whether an event must be reported to Quorum Review IRB, refer to the Safety Information and Unanticipated Problems Reporting Guideline. The Reporting Guideline includes a one-page summary with examples that can be posted in a convenient location.

Quorum Review IRB must review reports of Serious Adverse Events (SAEs). Please note that not all adverse events as defined by a research protocol need to be reported to Quorum Review IRB. Instead, only the events that meet the criteria below need to be reported. Quorum Review IRB defines an SAE as an adverse event that is:

1. Serious;
2. Unanticipated; and
3. Related to the study product or study procedures.

If an adverse event meets all three requirements, it is a reportable SAE. An “unanticipated” adverse event is one that is not identified in nature, severity, or frequency in the relevant safety documents(s) for the study product or is not identified as a possible risk in the study protocol or the informed consent form for the study. Investigators must report an SAE to Quorum Review IRB within ten (10) business days of becoming aware of the event’s occurrence. Please complete and submit Quorum Review IRB’s Safety Information and Unanticipated Problem Report form. An adverse event that does not meet all three reporting criteria listed above does not need to be reported to Quorum.

Major Protocol Deviations/Violations

A Major Protocol Deviation/Violation is any unplanned deviation from a Board-approved protocol that involves risk to research participants or others. It is the investigator's responsibility to assess whether a protocol deviation involves risk to the participant or others and submit all Major Protocol Deviations/Violations to Quorum Review IRB within ten (10) business days of becoming aware of the event's occurrence. Quorum Review IRB suggests that a protocol deviation involves risk where the protocol deviation adversely affects the:

- Safety or welfare of research participants or others;
- Rights of research participants or others; or
- Integrity of the study design.

Examples of Major Protocol Deviations/Violations include:

Inclusion/Exclusion	Study Drug/Device	Study Procedures	Informed Consent
* Participant enrolled in violation of inclusion or exclusion criteria	* Dosing error	* Omission or significant delay in performing study procedure	* Study procedures initiated before consent
	* Device malfunction	* Breach in safety monitoring procedures	* Person explaining informed consent did not sign/date on the same day as the research participant
	* Use of contraindicated medication or product		* Failure to use the most recent consent form
			* Deviation involved a vulnerable population (for example, child, illiterate, non-English)

A minor protocol deviation is a protocol violation that, in the investigator's judgment, does not adversely affect the risk/benefit ratio of the study; the rights, safety, or welfare of the participants or others; or the integrity of the study. Examples of *possible* minor protocol deviations may include:

- Study procedure conducted out of timeframe
- Study visit out of timeframe
- Participant failure to initial consent form
- Participant failure to return diary

NOTE: Minor protocol violations *do not* need to be reported to Quorum Review IRB.

Planned Protocol Waivers, Protocol Exceptions and Prospective Board Review

A site should obtain Board review prior to undertaking a planned deviation from the protocol that involves risks to participants or others, such as the planned enrollment of a participant in violation of the protocol's inclusion/exclusion criteria. Please refer to the section titled “Prospective Protocol Waivers” for information on this subject.

Unanticipated Problems

An Unanticipated Problem is any unfavorable event that occurs during the course of a research trial involving any aspect of the research trial. Unanticipated Problems may occur in clinical or non-clinical settings, and may relate to any particular persons, including research participants, research staff, or others. “Unanticipated Problems Involving Risks to Participants or Others” are events that occur during the course of a research trial that potentially increases the risk to participants or others; or adversely affects the rights, safety, or welfare of participants; or affects the integrity of a study. Investigators must report Unanticipated Problems to Quorum Review IRB within ten (10) business days of becoming aware of the event's occurrence.

Examples of possible Unanticipated Problems (other than Serious Adverse Events and Major Protocol Deviation/Violations) that should be promptly reported include:

- Research participant complaints
- Adverse audit or enforcement actions
- Breaches of privacy/confidentiality
- Unauthorized use or disclosure of protected health information (PHI)
- Loss of study records
- Disappearance of study drug
- Research staff misconduct affecting the research
- Incarceration of a research participant
- Injury sustained by research staff relating to the study
- Suspension of principal investigator's medical license
- Higher than expected volume of adverse events
- Higher than expected volume of protocol deviations
- Higher than expected volume of participant drop-out rates
- Complaint from a research participant involving an unanticipated risk that cannot be resolved by the research staff
- New findings that may influence a research participant's willingness to continue participation in the study

For more information on prompt reporting requirements and definitions, please refer to the Safety Information and Unanticipated Problems Reporting Guidelines on Quorum IRB's website.

Adverse Audit or Enforcement Actions

Investigators are required to promptly report as an Unanticipated Problem adverse audit or enforcement actions. This includes adverse findings from sponsor or regulatory audits such as Form FDA 483s, FDA Warning Letters, FDA Establishment Inspection Reports (EIRs), or sponsor corrective action plans.

The Board expects investigators to immediately implement corrective measures to address issues raised in adverse audits. Investigators should be aware that such issues, if not addressed, may lead to action by the Board including a finding of noncompliance or suspension of Board approval of the study. Please note that such findings require notification to the appropriate regulatory agencies.

Protocol Level Safety Information and Unanticipated Problems

Quorum Review IRB recommends that sponsors accept responsibility for submitting the following documents on behalf of investigators when such information qualifies as a Reportable Event:

- IND Safety Reports (i.e., external adverse events)
- Device Reports
- Data Safety Monitoring Board (DSMB) Summary Reports
- FDA or Sponsor Safety Alerts
- Notification of product withdrawals

- Recalls and clinical holds
- Other relevant safety information

Quorum Review IRB requests that the sponsor identify the party responsible for submitting study-wide safety information to Quorum Review IRB for investigators involved with the study on the “Central Study Questionnaire”. If the sponsor has assumed this responsibility, the sponsor will submit all protocol-level safety information to Quorum Review IRB at the same time these documents are sent to investigators. If the sponsor has not assumed this responsibility, each investigator will need to submit every reportable event to Quorum Review IRB.

Investigators can contact the sponsor or Quorum Review IRB with any questions as to whether the sponsor is submitting study-wide information on behalf of all investigators. In addition to submitting Reportable Events to Quorum Review IRB during the study, Quorum Review IRB requires the prompt submission of Reportable Events to Quorum Review IRB for at least two years after completion of the study if those Events directly affect the safety of former study participants.

Sponsor Reports of Changes to Investigator Brochures, Package Inserts, and Device Manuals

Quorum Review IRB requests that sponsors accept responsibility for submitting the following documents on behalf of investigators:

- Investigator Brochures
- Package Inserts
- Device Manuals

Revised Investigator Brochures, Package Inserts, and Device Manuals

Helpful Hints Submitting Safety Information
When submitting multiple reports simultaneously, sponsors and investigators are encouraged to include a cover letter listing all of the reports included in the submission. The Quorum Review IRB report form can be found on the website and should be completely filled out when submitting a Reportable Event.

When Investigator Brochures, Package Inserts, and Device Manuals are revised, Quorum Review IRB requires sponsors to submit a summary of changes along with the revised document to Quorum Review IRB on behalf of all investigators at the same time these revised documents are sent to investigators. In addition, it is especially helpful to provide a tracked version of the document showing the changes made.

Other Reports by Sponsors of Safety Information and Unanticipated Problems

In accordance with a sponsor's obligation to monitor investigators and their conduct of research, Quorum Review IRB expects the sponsor to promptly notify Quorum Review IRB in the event the sponsor becomes aware of a possible Unanticipated Problem or new findings detected during the monitoring process. This is true regarding events at the protocol level or the site level and could include evidence of serious or continuing noncompliance or evidence of scientific misconduct. Specifically, Quorum Review IRB asks sponsors to report events and findings not considered at the time of study design or consent form

preparation that could affect participants' safety or their continued willingness to participate, influence the conduct of the study, or alter the Board's approval to continue the study. Please note that reportable findings include relevant recommendations or findings of independent data monitoring committees. Quorum Review IRB will accept line listing of protocol level events that in and of themselves do not qualify as a reportable event. Line listings should include a summary of findings and recommendations for changes to study documentation (i.e. protocol and/or consent form).

Events That Do Not Meet Reporting Requirements

When a Reportable Event is submitted to Quorum Review IRB, Quorum Review IRB staff conducts a preliminary analysis of whether the event satisfies Quorum Review IRB's reporting criteria. If the submission does not qualify as a Reportable Event, then Quorum Review IRB staff will provide a standard acknowledgment and a brief explanation.

NOTE:
Quorum Review IRB recognizes that sponsors or sites may have operating procedures that require reporting of all events to the Board (regardless of whether Quorum Review IRB would require the reporting or not). Quorum Review IRB provides a standard acknowledgment of all documents submitted to fulfill such Sponsor and site requirements.

Please note also that the site **does not need to report to Quorum Review IRB** events that do not meet Quorum Review IRB's reporting requirements. Examples of such events may include:

- Minor protocol deviations (such as study visits performed slightly out of window);
- Adverse events that, in the investigator's judgment, are not related to the study;
- Adverse events that are anticipated or expected as part of the study;
- External Serious Adverse Event reports (for example, IND Safety Reports) that, in the investigator's judgment, do not adversely affect the conduct of the investigator's study at his/her research facility; or
- Research participant complaints that are adequately resolved by the research staff.

Investigators typically maintain records of all adverse events and protocol deviations that occur at the research facility. As a general rule, these records or logs do not need to be submitted to Quorum Review IRB. At the time of periodic site review, Quorum Review IRB's “Site Status Report for Periodic Site Review” will ask whether the investigator believes that a change in the research plan or the consent form is necessary in light of these unreported events. If the investigator recommends a change in the research or the consent form, Quorum Review IRB might request that the investigator submit the log or other summary of adverse events and protocol deviations for further consideration by the Board.

For more information, see the Safety Information and Unanticipated Problems Reporting Guideline. Additionally, Quorum Review IRB encourages all investigators and research staff to view Quorum’s online Safety Reporting Webinar. This webinar specifically clarifies safety information and unanticipated problems, and provides guidance on what, how, and when to submit such information to Quorum Review IRB.

Acknowledgment of Safety Information and Reportable Events

Quorum Review IRB provides three types of acknowledgment for Safety Information and Unanticipated Problems:

1. Standard Acknowledgment
2. Sponsor Acknowledgment Letters (sponsor distributes copies)
3. Sponsor Acknowledgment Letter with study-wide Safety Acknowledgment Letters (Quorum Review IRB distributes copies)

When Quorum Review IRB is reviewing a study on a single-site basis, Quorum Review IRB will always send the Standard Acknowledgment described below. When Quorum Review IRB is acting as a central Ethics Review Board, the sponsor determines the type of acknowledgment investigators will receive for study-wide reports at the time of protocol submission. The sponsor makes this choice on the "Central Study Questionnaire" form (CSQ).

- Standard Acknowledgment The investigator is responsible for submitting study-wide information as well as site-level information. Quorum Review IRB will send an acknowledgment of receipt to the site that submitted the material.

  In a multi-site study in which a number of investigators will submit duplicate information (such as IND safety reports), Quorum Review IRB will return a standard acknowledgment to each investigator who sends a submission.

- Sponsor Acknowledgment This type of acknowledgment is provided when a sponsor chooses to assume sole responsibility for submitting to Quorum Review IRB study-level safety information and Reportable Events (such as IND Safety Reports, Investigator Brochures, Package Inserts, and Device Manuals). Even if the sponsor assumes this responsibility, however, Quorum Review IRB will generate the acknowledgment letter upon receipt of the initial report without regard to who submitted it.

  Quorum Review IRB will generate only one receipt letter per report, even if Quorum Review IRB receives multiple copies of the report. In addition, Quorum Review IRB will generate a standard acknowledgment for each investigator who submits a copy of the report.

  On the CSQ the sponsor must choose how to have Sponsor Acknowledgment letters distributed to sites:
  - Option one – Sponsor Acknowledgment only: Quorum Review IRB sends the receipt letter to the sponsor only. The sponsor then accepts responsibility for distributing the letter to the sites.
  - Option two - Study-wide Acknowledgment: Quorum Review IRB distributes the receipt letter to each site that is open at the time of receipt. For this service, Quorum Review IRB will charge on a per site basis.

Please note that Quorum Review IRB's Safety acknowledgments represent receipt only; the acknowledgment does not represent Board review of the reported information. The Board will send a separate notice if it is determined upon review that additional action is necessary.

Investigators can contact the sponsor or Quorum Review IRB to determine what type of acknowledgment to expect for the study.

Data and Safety Monitoring

Under the federal regulatory structure, sponsors and investigators are required to monitor the progress of ongoing research, including the occurrence of adverse events. Federal regulations also require the IRB to determine whether the research plan makes adequate provision for the monitoring of the data collected to ensure the safety of participants. Accordingly, every protocol submitted to Quorum Review IRB for review must set forth a plan for the adequate monitoring of data throughout the course of the research.

Please note that Quorum Review IRB does not perform data monitoring (i.e., analysis of raw study data, case report forms, etc.). As an Ethics Review Board, Quorum Review IRB's role is to ensure the prompt reporting of certain Unanticipated Problems (see the section titled "Prompt Reporting Requirements" above). Quorum Review IRB will not approve a protocol that shifts responsibility for data monitoring to the Ethics Review Board. Quorum Review IRB also discourages sponsors and investigators from arranging for all adverse events to be submitted to Quorum Review IRB, as it is not Quorum Review IRB's role to review adverse events that do not qualify as Unanticipated Problems Involving Risk to Participants or Others.

In general, data and safety monitoring should be commensurate to the size, complexity, and level of risk involved in the research. For many research trials, a protocol that requires data and safety monitoring by the sponsor or investigators may be adequate. For other trials, however, the use of an external Data Monitoring Committee or Data and Safety Monitoring Board (both referred to hereafter as "DSMB") may be warranted.

Data Safety Monitoring Boards

A DSMB is a group of experts that meets on a regular basis to review the accumulating data and conduct of an ongoing clinical trial and advises the sponsor regarding the continuing safety of participants, as well as the continuing validity and scientific merit of the trial. While a DSMB may not be needed for every trial, a sponsor should consider establishing a DSMB in large, randomized, multi-site studies of long duration, particularly where the trial presents an elevated risk to participants or where interim analyses may be necessary to assure the scientific validity of the trial. For instance, a DSMB may be appropriate in a trial involving vulnerable populations with mortality or major morbidity as primary trial endpoints. In other cases, a DSMB may be needed to assess accumulating data so that the sponsor and investigators of research can remain unbiased and blinded to interim results.

When a DSMB is proposed by a sponsor, the Board may ask to review the composition of the DSMB, the affiliation of the DSMB members with the sponsor, if any, and the frequency with which the DSMB will meet. If this information is not included within the protocol the Board might ask to review the charter documents of the DSMB.

The Board requires the sponsor to provide Quorum Review IRB with reports of the DSMB meetings. These reports should be submitted at the time they are issued and will be requested at the time of protocol continuing review. Please note that the Board does not seek to receive data, either raw or summarized. Instead, the Board seeks the summary portions of such reports or the recommendations of the DSMB as to continuation of the study.

AMENDMENTS AND OTHER CHANGES TO RESEARCH ACTIVITIES

Board Review of Amendments

Most Amendment and Consent Form revisions that do not qualify for expedited review can be reviewed by a convened Board at one of Quorum Review IRB's Daily Meetings (which occur each weekday, excluding holidays). US amendments submitted by 5:00 p.m. PT are able to be reviewed within 36 business hours. Possible outcomes of review by the Board include:

- Approval The proposed change is approved as submitted. Approval documents are issued.
- Approval with modifications Modifications to the proposed change are required. The modifications must be submitted in writing for review and acceptance by the Board before any approval documents can be issued.
- Request additional information Further information is required before a determination can be made. Quorum Review IRB staff will follow-up with the investigator to request what is needed.
- Disapproval It is determined that the proposed change does not satisfy regulatory criteria for Board approval. The decision will be communicated in writing with the rationale for the disapproval. A decision to disapprove a proposed change may be appealed by responding with a formal written letter signed by the sponsor or investigator. All appeals must be reviewed at a convened meeting of the Board.

Changes in Research Activities

Sponsors and investigators are responsible for obtaining prospective Board review for changes in research activity. Examples of changes in research that should be submitted to the Board for review and approval include:

- Amendments and changes to the protocol (including administrative changes such as protocol clarification letters)
- Change in principal investigator
- Changes in the primary and/or additional research facilities (location move, suite number change, facility name change, etc.)
- Addition of research facilities for a previously approved investigator
- Changes in the investigator's conflict of interest status
- Notification of study completion/closure
- Planned increase in the number of participants to be enrolled in the study
- Changes in planned enrollment of vulnerable populations, including, but not limited to, employees and family members of employees, illiterates, and non-English-speaking participants
- Intentional departure from the inclusion/exclusion criteria set forth in the protocol when such variation affects the safety or welfare of study participants or affects the study integrity, even if the departure is approved by the sponsor (see the section titled “Prospective Protocol Waivers” below).

Please note that although prospective Board review and approval is required before implementing a change in research activity, the sponsor or investigator does not need to seek prior Board approval

before taking measures necessary to eliminate an apparent immediate hazard to research participants. This is consistent with the investigator's overarching obligation to promptly detect harm to participants and mitigate potential injuries (see the section titled "Prospective Protocol Waivers" below).

Changes to the Protocol and Revised Consent Forms

When Quorum Review IRB is the central Ethics Review Board for a multi-site study, the sponsor generally will submit changes to the protocol (e.g. amendments, protocol clarification letters, etc.) and model consent form revisions on behalf of all investigators or a sub-set of investigators. All proposed changes to an approved protocol must be submitted to the Board prior to implementation. In the case of single site studies, the investigator must submit all changes to the protocol and consent form revisions directly to Quorum Review IRB.

An illustration of Quorum Review IRB's process for the review of protocol amendments is available in the Protocol Amendment Review Illustration.

- The sponsor (or investigator in the case of a single site study) must forward a summary of changes (including rationale for making the changes) along with a copy of the amended protocol to the Board for review prior to implementation.
- If the change to the protocol requires subsequent revisions to the consent form, the sponsor (or investigator in the case of a single site study) must incorporate the revisions into the currently approved version of the consent form (see below). If the sponsor wishes to make consent form revisions beyond amendment-required changes, additional rationale for these changes must be submitted prior to Board review.

Sponsors must submit consent form revisions by "tracking" the revisions into the current Board-approved version of the consent form using the Microsoft Word track changes function. Alternately, Quorum Review IRB has a consent form revision service that will track revisions to the consent form on behalf of clients. Please contact Quorum Review IRB for additional details on this service or if you would like an estimate of charges or turnaround times. If the sponsor feels consent form revisions are not necessary, this should be communicated to the Board at the time of submission.

HELPFUL HINTS **Submitting Consent Form Revisions**
- Obtain an electronic version of the current Board-approved version of the consent form from the OnQ Client Portal.
- Edit the consent with the requested changes using the "track changes" feature in Microsoft Word.
- Include a written rationale with the revisions.

Typically, the Board reviews proposed changes to the protocol or consent form revisions that have been proposed by the sponsor or investigator. Occasionally, however, the Board may disagree with the proposed changes (or lack thereof). For instance, the Board may determine that a consent form revision is necessary where the sponsor or investigator did not propose such a change. Please note that in accordance with its authority to approve and require modifications in research, the Board may determine that changes to the protocol and/or consent form are necessary, even if not proposed by the sponsor or investigator. Quorum Review IRB typically will attempt to notify the sponsor prior to any Board review

that was not initiated by the sponsor or researcher.

Upon approval of changes to protocols, the Board will send a letter of Amended Approval to the sponsor and amended approvals to all investigators active in the study at the time of review. In the case of revised consent forms, participants who are currently enrolled and actively participating in the study should be informed of changes to a study if it might relate to the participants' willingness to continue their participation in the study. Quorum Review IRB considers active participation to include any intervention with a research participant including data collection.

Whether a particular change to a study might affect participants' willingness to continue participation in the study is the Board's prerogative to decide. However, the Board generally will not require reconsenting of participants who (i) have completed their active participation in the study, or, (ii) are still actively participating in the study, but the change will not affect their participation (e.g., the change is the addition of a study procedure that will be implemented only for subsequently enrolled participants). With respect to the reconsenting of participants with revised consent forms, the Board will provide instructions for reconsenting when the Board issues approvals for the revised consent forms.

Prospective Protocol Waivers

As a general rule, an investigator must obtain prospective Board review and sponsor approval of any intentional deviation from the protocol that involves risks to participants or others before implementation of the change. This is true even if the sponsor has approved the deviation. (For other changes to previously reviewed research see the section titled “Changes in Research Activities.”)

Changes in Approved Research Deemed Necessary to Eliminate an Apparent Immediate Hazard

Generally speaking, an investigator may not initiate a change in research activity unless he/she has received Board approval of the change. However, an investigator is entitled to make changes to the approved research without prospective Board review when the change is necessary to eliminate apparent imminent hazard to research participants. If the change is a Major Protocol Deviation/Violation, the investigator should report the incident according to Quorum Review IRB's Safety Reporting Guidelines.

Planned Deviation in the Absence of a Hazard

If an intentional deviation to the Board-approved protocol is desired for an individual research participant (other than to eliminate an immediate hazard), an investigator must request a protocol waiver or exception from the sponsor and obtain prospective Board approval. To initiate Board review of a Protocol Waiver/Exception, the investigator should submit a request for prospective Board approval and sponsor approval according to the Safety Reporting Guidelines. Please note that written documentation of sponsor's approval of the Protocol Waiver/Exception is a requirement before the Board will review the request. Furthermore, to the extent investigators or sponsors desire protocol waivers/exceptions for multiple research participants, the Board may determine further action is necessary such as a formal change to the Board-approved protocol.

Note: Board approval of a Protocol Waiver/Exception request is a significant matter and requires special attention. An investigator should not assume that Board approval will be granted. To that end, Quorum Review IRB strongly advises sites not to schedule participants for the study activities represented in the Protocol Waiver/Exception request until after the Board provides notification of approval. Quorum Review IRB also strongly advises investigators to obtain sponsor approval and submit the Protocol Waiver/Exception request to Quorum Review IRB as far as possible in advance of the proposed scheduling timeline for the participant.

Research Staff and Research Facility Modifications

Guidance documents and necessary forms for submitting study site modifications to Quorum Review IRB can be found at www.QuorumReview.com

In order to ensure proper documentation and prompt review and approval of any changes to research staff or research facility information made during the course of any study, please follow the instructions below. This will allow for thorough and accurate documentation for both Quorum Review IRB and the investigator.

Any change in approved research site information must receive Board review and approval prior to implementation, with the exception of a new phone/fax number or study coordinator/contact. Therefore, Quorum Review IRB requests that all documentation be received by Quorum Review IRB at least two weeks prior to instituting the change(s) to allow for necessary administrative processing time and Board review.

Change in Phone Number / Fax Number

- Notify Quorum Review IRB via the "Change Request Form for Sites" of telephone, fax, or other contact information changes prior to implementation, if possible.

Change in Study Coordinator / Primary Study Contact

- Notify Quorum Review IRB via the "Change Request Form for Sites" prior to research staff changes, if possible.
- Please include the full name, titles, and phone number/fax number associated with this change.
- Please note: Changes to and/or deletions involving sub-investigators do not need to be reported to Quorum Review IRB unless the sub-investigator fulfills a specialist requirement as part of the protocol.

Change of Research Facility Address

- Update and submit a revised "Site Information Questionnaire" form, "Change Request Form for Sites" or "Additional Research Facility Site Information Questionnaire" form, as appropriate.

Addition of New Research Facility

- Notify Quorum Review IRB via the "Change Request Form for Sites" and an updated "Additional Research Facility Site Information Questionnaire" form.
- Indicate whether the additional facility's address should be added to the consent form(s). If not indicated, Quorum Review IRB will not revise the consent form(s) to include additional addresses.

Deletion of a Research Facility

- Notify Quorum Review IRB via the "Change Request Form for Sites".
- If the research facility being removed is listed on the current consent form, Quorum Review IRB will revise the consent form to delete that address and will issue a revised consent form to the investigator following review and approval of the information.

Change in Principal Investigator

Quorum Review IRB treats a change in principal investigator very similarly to an initial site submission. A change in principal investigator must be reviewed by the Board and cannot be submitted for review until all of the following documents are received:

- A letter from the current principal investigator explaining why he/she is no longer able to perform the role of principal investigator.
- "Change Request For for Sites" signed by the new principal investigator for the primary facility.
- A current (within two years), dated CV for the new principal investigator. The CV must describe the person's education, licensure (for all states in which the research is being conducted), training, clinical background, and research experience relevant to the study in question. If the principal investigator's relevant research experience is not included in the CV, please provide additional documentation as necessary.
- Supplemental material as appropriate based on the "Change Request Form for Sites" responses (for example, FDA audit information, letters of explanation, etc.).

PROTOCOL CONTINUING REVIEW / PERIODIC SITE REVIEW

An illustration of Quorum Review IRB's process for periodic review is available in the Continuing Review Flowchart

At the time of initial review of research, the Board establishes an approval period for an approved study. Regulations require continuing review of the research at least once per year and more frequently if determined necessary by the Board. The expiration date of an investigator's Board approval will be noted on the "Notice of Approval," any subsequent "Amended Approvals," and on the "Site Status Report."

Sponsor's Role

When Quorum Review IRB is acting as a central Ethics Review Board, Quorum Review IRB will send the sponsor a continuing review packet that will include a copy of the "Protocol Continuing Review Report" and a copy of the materials provided to sites for periodic site review. When Quorum Review IRB is not the central Ethics Review Board for a multi-site study, Quorum Review IRB will send the reminder and report form to the investigator who then must forward it on to the sponsor. Sponsors must return the "Protocol Continuing Review Report" by the due date indicated on the form so that the protocol can be reviewed prior to the site review.

Investigator's Role

In order for Board approval of a study to be extended beyond the current approval period's expiration date, the Investigator must submit a completed "Site Status Report for Periodic Site Review" form for the site (and, sometimes, for the sponsor – see above). The report must be submitted by the due date noted on the "Notice of Approval." Quorum Review IRB will send a partially pre-populated "Site Status Report" form to the site approximately two (2) months before the approval expiration date. The completed form should be returned to Quorum Review IRB at least six (6) weeks prior to the approval expiration date to allow adequate time for Board review.

A completed "Site Status Report" form must be returned to Quorum Review IRB before the site's expiration date to indicate that site is either undergoing periodic site review or closing. For more information about when a "Site Status Report for Closing" can be submitted, see the section titled "Study Closure" in Chapter 9.

Quorum Review IRB staff follows up with investigators who have not submitted "Site Status Report" forms by the due date. Quorum Review IRB will fax, call, and send an expiration warning letter to the investigator (with a copy to the sponsor) in an effort to assist the investigator and avert an unintended expiration.

HELPFUL HINTS
FAQ: Periodic Site Review Please see the Site Status Report FAQ for assistance in preparing investigator periodic site review materials.

For common investigator questions about “Periodic Site Review,” please see the “Periodic Review and Site Closure Frequently Asked Questions” document on Quorum Review IRB's website.

It is important to promptly comply with re-approval requirements. The consequences of allowing Board approval to expire are serious and might include notification to the appropriate regulatory authorities. All research activity must be terminated upon expiration of Board approval.

STUDY CLOSURE

Federal regulations require that the investigator notify the Board of all changes in research activity. Study closure qualifies as a change in research activity that requires notice to the Board. Quorum Review IRB thus requires investigators to provide formal notice of closure in all instances, including premature study termination or cancellation by the sponsor.

To ensure that all required information is included in the notification of closure, the use of Quorum Review IRB's standard "Site Status Report for Closing" form is required.

The "Site Status Report for Closing" form must indicate that the following criteria have been met:
* No actively enrolled participants;
*No data collection from participants (including follow-up calls); and
*The site has been closed by the study sponsor or sponsor representative

Quorum Review IRB considers a study closed at a site only if there are no actively enrolled participants and all interventions with participants have ceased. Please note that being "closed to enrollment" does not meet Quorum Review IRB's definition of study closure.

Once all participants have completed a study and all interventions with participants have ceased, Quorum Review IRB considers the date of study closure to be the date on which a representative of the sponsor administratively closes the study at the research site. Quorum Review IRB will not accept "Site Status Report for Closing" forms that are received before the date of study closure.

Quorum Review IRB will send the investigator and sponsor a letter of acknowledgment of site closure. Although Quorum Review IRB will accept further information submitted for a closed research site, no approvals of additions or changes to research activities will be issued.

In the rare instance that a site is unable to complete the Quorum Review IRB "Site Status Report for Closing" form but the sponsor considers the site to be closed, Quorum Review IRB will accept documentation from the sponsor confirming:

- The site never initiated study activity, or the date of site closure by the sponsor or sponsor representative;
- That there are no enrolled participants at the site;
- That the site is no longer collecting data from participants; and
- The reason for non-responsiveness by the site.

Quorum Review IRB does not consider a protocol closed until all Quorum Review IRB-approved sites have been closed by the sponsor or the sponsor's representative, submitted valid Quorum Review IRB "Site Status Report for Closing" forms, and been administratively closed out by Quorum Review IRB staff. Once all sites have been closed, Quorum Review IRB will close the protocol. Quorum Review IRB does not send sponsors written documentation of study closure.