13. Overview of WIRB's continuing review activities and reports

A. Continuing Review

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

FDA regulations regarding continuing review require an IRB to conduct continuing review of the research at intervals appropriate to the degree of risk, but not less than once per year [21 CFR § 56.108 (a)(1) and § 56.109(f)]. Beginning in May 2009, for most types of research, the Board requires two reports per approval period, and conducts full board re-review annually. For a few types of research, however, full board review is conducted more frequently than once a year. The Board normally determines that a full review of phase I research, investigator-initiated single-site interventional studies of investigational drugs and devices, emergency research conducted under 21 CFR 50.24, and child research conducted under 45 CFR 46.407 should be conducted every six months. The Board may also direct more frequent than annual review for other research as deemed appropriate. Sites approved for 6 months at a time should expect to receive and complete four reports per year (two for each six month approval period).

Completed Continuing Review Report Forms (CRRFs) provide WIRB with the study-related data necessary to monitor the progress of the research at sites. WIRB sends sites a CRRF three weeks prior to the due date, according to the frequency established by the Board. Identifying information including investigator name, sponsor name, protocol number and the "sequence" number of the form is listed at the top of each form. The due date is also listed at the top of the form. Over the course of a year, studies assigned to a two per period reporting cycle will receive one "Interim" CRRF and one "Study Renewal" CRRF. The Study Renewal CRRF is sent out approximately 50 days before the study's expiration date, in order to ensure it is completed and sent back to WIRB before the Board conducts the study renewal review. The Board may take action to suspend or terminate approval of the research if reports are not accurately completed and returned promptly.

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

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

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

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

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

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

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

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

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

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

4. *Provide the following enrollment numbers:*

"Screen failures" signed the consent form, but later proved not to qualify for the study during screening procedures.

Subjects in screening (consented, not yet active)	+ Subjects active	+ Subjects in follow-up	+ Withdrawals* (include any deaths)	+ Screen failures* (consented)	+ Subjects completed*	= Total Subjects consented*

Subjects in follow up participate in monitoring activities only, such as surveys or phone calls to check their status (subjects receiving treatments or procedures such as blood draws, adjustments of devices, blood pressure checks and so forth are considered active).

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

** Cumulative total from start of study*

The reported number of total subjects consented cannot decrease over time.

5. *Number of females consented* _____

6. *Number of racial minorities consented: _____*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

New team members must complete human subject protection training.

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

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

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

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

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

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

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

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

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

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

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

If yes, attach appropriate information.

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

24. Signature of PI or designee.

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

ii. Delinquent CRRFs

Seven days before the due date, a CRRF labeled "Reminder Notice" is mailed to the site. If a completed CRRF is not returned to WIRB, WIRB sends the site a second copy of the missing CRRF labeled "Reminder Notice." The Board may take action to suspend or terminate approval of research if reports are not accurately completed and returned promptly. If WIRB suspends or terminates the study, at a minimum, the investigator and sponsor will be notified of the Board's action, as well as any federal agencies with jurisdiction over the research, such as FDA and/or OHRP.

When a CRRF is not returned by the due date printed on it, WIRB takes the following action:

1. If no response is received 7 days after the due date, WIRB staff prepare a "past due" letter which explains that if a satisfactory response is not received within 10 days, the delinquency will be reported to the Board and that the Board may take

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

2. If no response is received 17 days after the due date on the CRRF, WIRB staff place a courtesy call to the sponsor notifying them of the continued delinquency and the likelihood that the Board will take action to suspend the study at the site if a response is not received.
3. If no response is received 24 days after the due date on the CRRF, the delinquency is reported to the Board. If the Board suspends the study, WIRB is required to report the suspension to the appropriate federal agency or agencies (FDA, OHRP, etc.) If the suspended investigator is at an institution which has notified WIRB that they will self-

   report these actions to the appropriate agency or agencies, the institution will receive a notification of the Board's action and a cover letter reminding them of the reporting requirement. The institution has 30 days to then report to the agency and copy WIRB.

iii. Signed Consent Form Requirement:

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

iv. Definition of Screen Failures and Withdrawals

Report the number of screen failures and withdrawals on the CRRF according to the following definitions.

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

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

v. Study Renewal

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

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

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

B. Study Closure

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

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

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

In May 2006, WIRB began sending closure confirmation notices to all study contacts upon receipt of a study closure form. Sites must have active on-going IRB approval in order to enroll subjects, perform any study interventions, collect/report new data, and/or, if under an FWA, analyze identified data at the site. If you receive a closure confirmation for a study you believe was closed in error, contact WIRB immediately to avoid a substantial gap in IRB oversight for the research.

Board may conduct renewal review of a site up to 30 days prior to the study expiration date listed on the Certificate of Approval. **Review fees apply for the study renewal service** and review is carried out if WIRB does not receive a study closure notice *prior to renewal of the study* (which, for logistical reasons, may be scheduled up to 30 days before the study expiration date). To avoid unnecessary reviews and fees, do not delay reporting a study closure to WIRB if the expiration date is approaching.

C. Site Visits

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

During site visits, the WIRB representative will focus on subject safety as well as regulatory compliance. The visits also offer an opportunity to the site to address research-related issues and ask questions of the WIRB visitor.

In preparation for the visit, WIRB asks the sites to set out the following review materials in a suitable work area, to allow for the visit to be conducted efficiently and with minimal disruption to the site's work:

- The site's informed consent policies, and the process by which consent is routinely obtained.
- The site's document files for WIRB-approved studies, including:
  - Protocol and amendments,
  - IRB correspondence and approved consent form(s),
  - Participant charts or source documents and the consent form(s) for each study,
  - Investigator Brochure(s),
  - Curriculum Vitae (CV) for all research staff, and
  - The Principal investigator's CV and medical license.

WIRB may also ask to see the site's drug storage areas and emergency equipment.

WIRB conducts the following types of site visits:

- Routine (Site Assessment) – Routine site visits are generally brief and simple. However, some “routine” visits to sites at institutions with which WIRB has a contract are dictated by the terms the contract, and those visits’ length and depth will vary depending on the terms in the contract.
- For-Cause – WIRB staff initiate “for-cause” site visits in response to concerns raised about the site, investigator, etc. These visits are usually carried out by WIRB Regional Representatives, Board members or WIRB management.
- Board-Directed – The Board directs site visits in response to concerns raised about the site, investigator, etc. These visits are usually carried out by WIRB Regional Representatives, Board members or WIRB management.

Sites receive a site visit confirmation notice soon after the site visit has been scheduled. The notice provides the time of the visit, the basis for the visit, the name of the visitor and the agenda for the visit.

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

- Credentialing –

Credentialing has significant benefits for investigators and research staff, including a significant reduction in the time and energy it takes to complete submission. Every time an investigator becomes credentialed, the Board can have confidence that the investigator has the right processes in place and sufficient knowledge to protect subjects enrolling in research at his or her site. Credentialed investigators who choose to may be included on a list of credentialed investigators that will be provided to sponsors and CROs.

Requirements
Credentialing involves an onsite visit by a WIRB professional who provides training, gathers information about the investigator and research staff, and reviews standard operating procedures. During this time, investigators will be given direct input on how to best comply with regulations and ethical standards. Once the credentialing visit is completed, a report will go to the Board for review and the Board will decide whether to award credentialed status to the investigator. WIRB will maintain a database of credentialed investigators and will make periodic contact to see if there have been any changes.

Costs
There is no fee for this service. We believe that offering this service will promote subject safety and result in faster turnaround time for review of submissions.

Getting started
To learn more about WIRB's investigator credentialing, contact us.

14. Fees

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

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