WIRB imposes the following limitations on generic consent forms:

- Pre-study screening done outside of a specific research protocol should be limited to minimal risk procedures.
- Current treatment or medications should not be adjusted in order to do the screening.

Accordingly, prospective subjects should not undergo a washout or biopsy as a generic pre-screening activity; instead, the subject should be fully consented for the related protocol before beginning that protocol's screening activities.

B. Generic Advertisements

WIRB reviews "generic" advertisements linked to a company or an investigator and protocol-specific generics that do not contain any site-specific information. Approval documents for generic advertisements are transmitted to the submitter; courtesy copies of generic advertisements will not be distributed to multiple sites or investigators.

Unless subjects at all sites (and/or participating in all protocols) receive the same payment for every study visit, it is wise to omit dollar amounts from generic advertisements. A general statement such as "subjects will be paid for their participation" is recommended instead.

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

C. Expiration and Renewal of Generic Materials

Approved generic items are generally valid for one year. When the anniversary date approaches, WIRB staff will contact the submitter and inquire if renewal is desired. WIRB will conduct an annual review of the item if a response is not received by the date cited in the correspondence to ensure continued use is valid and under IRB oversight. Study Renewal Review fees apply. Expired generic items cannot be used. To prevent unnecessary renewal reviews, notify WIRB when use of the generic material has ended.

Occasionally, the Board may modify an item during the renewal review, usually due to changes in regulatory guidance or Board policy. Board-directed modifications are indicated in the approval documentation provided to the submitter.

12. WIRB reporting requirements for unanticipated problems

Federal Regulation 21 CFR §56.108 (b) (1) and 45 CFR 46.103(b)(5) require the IRB to "follow written procedures for ensuring prompt reporting to the IRB…any unanticipated problems involving risk to human subjects or others." WIRB's expectations for reporting of unanticipated problems are described below.

An unanticipated problem is defined as any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the drugs, devices or procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Device reporting requirements are similar, but differ slightly: The device regulations use the term “Unanticipated Adverse Device Effect” (UADE), which is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))

All reports to the IRB of unanticipated problems should explain clearly why the event is "unanticipated" and clearly explain why the event represents a “problem involving risks to human subjects or others.”

WIRB expects reports to the IRB of unanticipated problems to include a corrective action plan to address the issue, or written justification for why an action plan is not provided.

Sites often ask why WIRB requires a corrective action plan with reports of unanticipated problems, since the regulations do not specifically require a corrective action plan. An adverse event or protocol variance is considered to be an unanticipated problem if it suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized. If this is the case, WIRB has an ethical responsibility to ensure a corrective action is proposed that will minimize the risk or at least inform subjects about the increased risk (so that they can make a decision about whether to continue to participate in the research). Possible actions taken to minimize the risk might include (but are not limited to) a change in the inclusion or exclusion criteria, addition of new safety monitoring, a change to the administrative processes at the site, or the addition of information about the increased risk to the consent form.

For more information about corrective action plans for unanticipated problems, consult the OHRP guidance titled “Guidance on Reviewing and Reporting Unanticipated

Problems Involving Risks to Subjects or Others and Adverse Events" available here: http://www.hhs.gov/ohrp/policy/advevntguid.html.

Please note that unnecessarily reporting problems that do not meet the criteria outlined above may impair the Board's ability to review and respond in a timely manner to actual situations where subject rights, welfare or safety are threatened.

A. Unanticipated Problems that are Adverse Events:

Adverse events are any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

FDA guidance documents recognize that:

1. "individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered to be an unanticipated problem," and
2. "All reports to the IRB of unanticipated problems should explain clearly why the event described represents a 'problem' for the study and why it is 'unanticipated.'"

FDA believes that reports that lack such evaluation should not be provided to the IRB.

The reporting requirements for WIRB may differ from the reporting requirements for the sponsor. Report to WIRB only adverse events that in the opinion of the investigator may **represent unanticipated problems involving risks to the other subjects in the research**.

i. Adverse events that are determined to be unanticipated problems occurring at your site:

Use the Report Form for Unanticipated Problems that are Adverse Events to report an unanticipated adverse event that occurred at your site.

Investigators are required to report adverse events that fit the following criteria *within 10 working days* of the time the investigator becomes aware of them:

- Event is **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, or the Investigator Brochure; and (b) the characteristics of the subject population being studied,
- **Related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research **places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

If the adverse event is clearly not related to the study drug, device, procedures, or washout process, it would not represent a risk to other subjects in the research or a "problem" for the study and, therefore, does not have to be reported to WIRB.

ii. Adverse events that are determined to be unanticipated problems that did not occur at your site (non-site adverse reports such as IND safety reports, SUSAR reports, and so forth):

WIRB will accept non-site adverse event reports submitted by investigators and from sponsors on behalf of investigators, if, in accord with 21 CFR 312.32,

- the event described is both serious and unexpected,
- the report identifies all previous safety reports concerning similar adverse experiences,
- the report analyzes the significance of the current adverse experience in light of the previous reports, **and**
- the report outlines a corrective action plan (such as a consent form or protocol change).

WIRB will not accept non-site adverse events that do not identify all previous safety reports concerning similar adverse experiences, analyze the significance of the current adverse experience in light of the previous reports and outline a proposed correction action plan. These submitted reports will generally be returned to the submitter with a description of the WIRB reporting requirements and guidance encouraging the submitter to resubmit with the required analysis.

If you have arranged for the sponsor to report the unanticipated problem directly to WIRB, we do not expect you to provide us with a duplicate copy of the report received from the sponsor.

If the sponsor, CRO or SMO does not submit non-site adverse events that are determined to be unanticipated problems to WIRB on behalf of your site, you are required to submit them, **along with the required explanation outlined above**, within 10 days of the date you receive them.

WIRB recognizes that for multi-center studies, the sponsor is in a better position to process and analyze adverse event information for the entire study, and to assess whether an occurrence is both "unanticipated" and a "problem" for the study. Accordingly, you may rely on the sponsor's assessment and provide to WIRB a report of the unanticipated problem prepared by the sponsor.

B. Unanticipated Problems that are Not Adverse Events

Use the Report Form for Unanticipated Problems that are Not Adverse Events to report the following unanticipated problems:

- Unanticipated problems that do not fit the definition of an adverse event, but which may, in the opinion of the investigator, involve risk to the subject, affect others in the research study, or significantly impact the integrity of research data. For example, report occurrences of breaches of confidentiality, accidental destruction of study records, or unaccounted-for study drug.

- *Unplanned* protocol deviations/violations that have already occurred, that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data, AND for which you did not seek WIRB pre-approval.

Report occurrences within 10 days of becoming aware of them.

Note: *Planned* protocol deviations
Due to differing regulatory requirements, WIRB reporting requirements for planned protocol deviations differ depending on whether your research federally funded or is covered by a federal-wide assurance (FWA):

- If the research is **not** federally funded and the research is **not** conducted under an FWA, planned protocol deviations that may adversely affect the rights, safety or welfare of subjects or the integrity of the research data should be submitted to WIRB for review and approval **prior to implementation** except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].
- If the research **is** federally funded or **is** conducted under an FWA, **all** planned protocol deviations must be submitted to WIRB for review and approval **prior to implementation** except where necessary to eliminate apparent immediate hazards to the human subjects [(DHHS 45 CFR § 46.103(b)(4); (FDA 21 CFR § 56.108(a)(4); ICH 3.3.7].

The reason for these different requirements regarding planned protocol deviations is that the Office for Human Research Protections (OHRP) has adopted the regulatory interpretation that every planned protocol deviation is a change in research that needs prior IRB review and approval before implementation. However, the Food and Drug Administration (FDA) has not adopted this interpretation.

Use the **WIRB Change in Research and Subject Recruitment (Ads) Submission Form** to request approval of a planned protocol deviation prior to implementation. (Deviations necessary to eliminate apparent immediate hazards to the human subjects should be reported within 10 days on the WIRB **Report Form for Unanticipated Problems that are Not Adverse Events**.)