

 JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH	Human Research Protection Program Policies & Procedures	
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Title: Unanticipated Problems and Adverse Events	Date Effective 01/31/05	Supercedes P&P dated 12/09/04

BACKGROUND

Unanticipated Problems

HHS and FDA regulations require that IRBs review “unanticipated problems that involve risks to research subjects or others” and have procedures for appropriately informing Federal department or agency heads when these occur. The term “unanticipated problems” is, however, not consistently defined by the Federal regulations, sponsors and other institutions. For studies that it reviews, CHR defines an unanticipated problem as:

“a harmful or potentially harmful occurrence that is reasonably related to the conduct of the study, not expected by the researchers (i.e., not an expected AE described in the study protocol, consent form or investigator’s brochure), and that may affect either the research subjects or others. “

Unanticipated problems may occur at the research site or elsewhere, and in all types of studies, including observational studies, behavioral intervention studies and clinical trials. Unanticipated problems that involve risk to study subjects or others must be reported promptly to CHR. Following review of the problem CHR may require corrective actions.

Adverse Events

The term “*adverse event*” does not appear in Federal regulations. It is, however, widely used to describe undesirable effects associated with interventions, especially in FDA-regulated and industry-sponsored clinical trials. For clinical trials and behavioral intervention studies that it reviews, CHR defines an adverse event (AE) as:

“an unfavorable event associated with a study intervention or with other study procedures. Examples include toxic or allergic reactions to an experimental drug, a complication from use of a medical device, significant emotional distress or exacerbation of an existing mental disorder.”

CHR also uses the following additional definitions:

Serious adverse event (SAE): An adverse event that causes death, is life-threatening, requires inpatient hospitalization or prolongs existing hospitalization, causes a persistent or significant disability or incapacity, causes a congenital anomaly or birth defect, or, in the judgment of the investigators or safety monitors, significantly increases risk to study subjects.

Expected adverse event: An adverse event that is expected, based on previous studies of the intervention, and is described in the consent form, the study protocol or the investigators brochure.

These also include adverse events that are recognized for the first time during the conduct of a trial and, after review by CHR and/or the DSMB, are not considered to require that the trial be stopped or the intervention be modified. Further occurrences of these events during the trial are then classified as expected adverse events.

Adverse events may be noted during or following an intervention. Detecting and reporting adverse to study sponsors and regulatory authorities, and assessing their relation to the intervention, is a necessary part of the evaluation of the safety of an intervention. Adverse events that may be reasonably expected as a result of study procedures should be described in the consent form and the study protocol. The protocol should also describe how adverse events will be monitored, reported and analyzed.

JHSPH POLICY AND PROCEDURES

Reporting Unanticipated Problems

What Needs to Be Reported

An event that must be reported promptly includes any event, occurring on-site or off-site, that in the opinion of the Principal Investigator or Safety Monitor:

- was unanticipated, and
- involved risk to study subjects or others, and
- was reasonably related to the conduct of the study.

Examples include:

- an AE or SAE that is more severe than expected;
- an AE or SAE that is determined by the DSMB to occur more frequently than expected;
- a computer containing identifiable data is lost, creating a risk of breach of confidentiality and placing study subjects at risk of emotional or social harm;
- a study medication is given incorrectly causing toxic effects;
- a study subject threatens to harm himself or others;

- a diagnostic test is carried out incorrectly and fails to detect a treatable condition; as a result subjects do not get the benefit of effective treatment; and
- an accident occurs at the study site and several subjects are injured.

Unanticipated problems that are possibly or probably related to study procedures should be reported regardless of whether they occur during the study, after study completion, or after the affected subject has completed participation or is no longer enrolled in the study.

Who Should Make the Report

Reports of unanticipated problems are usually made by the Principal Investigator. They may, however, come from any source, including CHR members, other investigators, Study Safety Monitors, research subjects or their family members, JHSPH personnel or others. When a problem is first recognized by, or reported to, the Principal Investigator it is his or her responsibility to inform the ORS and, if appropriate, the study sponsor.

When and How to Report

Reports should be made on the [CHR reporting form](#) or a sponsor's form, provided it includes all information requested by the CHR form. Reports are sent to ORS and, for Federally supported research, to the funding agency. Reports may also be required by the FDA and other study sponsors.

- Report within 10 days of being detected:
 - Death of a subject, unless study subjects are expected to have significant mortality from their underlying condition and *any connection* between study procedures and the subject's death has been ruled out. Where doubt exists, however, the death should be reported.
 - Unanticipated problems, other than death, that increase risk to study subjects or others;
 - Expected adverse events that are more severe than described in the consent form, study protocol or investigators brochure (see below); and
 - Expected adverse events that occur more frequently than described in the consent form, study protocol or investigators brochure (see below).

Note: Events that are *expected* and *clearly due* to the natural progression of the subject's underlying disease or condition need not be reported; however, where doubt exists and the event is serious, it should be reported.

Reporting by Multi-Site Studies and Coordinating Centers

- Multi-site Studies. For multi-site studies in which the Principal Investigator is a JHSPH faculty member and CHR serves as the IRB, the reporting of unanticipated problems is the same as for single-site studies. If the problem occurs at a non-JHSPH site, it must

be reported to the local IRB according to local IRB regulations *and also* reported to ORS.

For multi-site studies in which JHSPH does not serve as the IRB, CHR does not need to receive or review individual reports.

- Coordinating Centers. When JHSPH serves as the coordinating center for a multi-site study, but there is no subject contact and no data collection done by JHSPH staff, unanticipated problems should be reported to the IRBs for the individual sites. CHR does *not* need to receive or review the reports.

Monitoring and Reporting of Adverse Events

Monitoring for AEs and SAEs.

Clinical trials and behavioral intervention studies that are *greater than minimal risk* must have a plan for detecting and reporting AEs and SAEs. Depending on the level of risk and the study design, safety monitoring may be done by a designated investigator in the study, an independent Study Safety Monitor, Safety Monitoring Committee, or a Data and Safety Monitoring Board (DSMB):

- A DSMB is *required* for phase III controlled clinical trials in which mortality or major morbidity are primary or secondary endpoints, or where these outcomes are likely even when the study addresses lesser outcomes, such as the relief of symptoms.
- A DSMB should be *considered* for:
 - phase I and II clinical trials that have multiple study sites, are blinded, employ moderate or high-risk interventions, or involve vulnerable populations;
 - trials in which a DSMB can help ensure scientific validity, for example by performing interim analyses that may lead to revision of the trial design, and for
 - behavioral intervention studies that involve vulnerable populations or in which serious adverse events related to the intervention or study procedures are possible.
- At a minimum, *phase I and II clinical trials* that are greater than minimal risk require an independent Study Safety Monitor.
- Safety monitoring by an independent Study Safety Monitor or a designated investigator is appropriate for most *behavioral intervention studies*.

Safety Monitoring Plan.

The Research Plan for clinical trials and behavioral intervention studies with greater than minimal risk must describe the following:

- who will perform safety monitoring, and their affiliation and expertise;
- the safety endpoints (i.e. AEs and SAEs) to be monitored;

- the frequency of review by the Safety Monitor or DSMB of aggregate summaries of expected AEs and SAEs (this should be based on the level of risk associated with the study and the nature of expected AEs and SAEs);
- the plan for promptly providing to CHR the reports of all safety monitoring reviews of AEs and SAEs, and
- the plan for reporting to CHR within 10 days of being identified any expected AEs or SAEs that occur *more frequently*, or are *more severe*, than described in the consent form, study protocol or investigator's brochure.

For DSMBs, the plan should, if possible, be developed with input from the DSMB chairperson and should *additionally* describe:

- the membership of the DSMB, clearly specifying independent (i.e. voting) members and non-voting members, their affiliation and expertise;
- the schedule of DSMB meetings, including a provision for emergency meetings, if required,
- the timing of any proposed interim analyses;
- rules for stopping the study because the intervention is proven effective, ineffective or unsafe, or because the study does not have sufficient power to achieve a meaningful assessment of the intervention; and
- plans for promptly providing all DSMB reports to CHR.

A detailed discussion of the role, composition, and function of a DSMB can be found at <http://www.fda.gov/cber/gdlns/clindatmon.htm> .

The CHR may decide, on a case by case basis, the type of safety monitoring and the frequency of review of adverse event reports required for a specific study.

Who May Serve as Study Safety Monitor or as Members of a DSMB?

Study Safety Monitor. The Study Safety Monitor is usually proposed by the Principal Investigator or study sponsor. He or she must have appropriate expertise for detecting and assessing AEs, and determining their possible relation to interventions used in the study.

DSMB. The chairperson of the DSMB may be appointed by the study sponsor or proposed by the Principal Investigator; members should be agreed by the chairperson. A DSMB usually has at least three independent voting members, including the chairperson, with expertise in the conduct of clinical trials, biostatistics and research ethics. Larger, more complex trials require a larger membership with a wider range of skills. For clinical trials one voting member of the DSMB should be certified in Good Clinical Practice or the equivalent. Representatives of the study sponsor and the research team may also serve on the DSMB, but only as non-voting members.

Conflict of interest. The Study Safety Monitor and voting members of the DSMB should have no other role in the study and should be selected to avoid real or perceived financial, professional or personal conflicts of interest. Examples of individuals with conflicts include:

- individuals employed by, or with a financial interest in, the company supporting the study or producing a product being evaluated,
- persons who serve as academic advisors to, or are the supervisors or teachers of, any of the investigators,
- persons who are investigators on related studies,
- individuals who are related by blood, marriage or other significant relationship to an investigator on the protocol, and
- individuals whose professional advancement is determined to an appreciable extent by one of the investigators.

Reporting Adverse Events

- Report to CHR as described above for unanticipated problems:
 - Death of a subject, unless study subjects are expected to have significant mortality from their underlying condition and *any connection* between study procedures and the subject's death has been ruled out. Where doubt exists, however, the death should be reported; and
 - Expected AEs and SAEs that are *more severe*, or are determined by the Safety Monitor or DSMB to occur *more frequently*¹, than described in the consent form, study protocol or investigator's brochure.
- Report to the Study Safety Monitor or DSMB:
 - All *expected* AEs and SAEs according to the agreed reporting schedule and format².

Note: Expected AEs and SAEs do *not* need to be reported to CHR, unless they occur with unexpected frequency or increased severity, as described above. Investigators may, however, be required to report *all* AEs and SAEs to study sponsors and Federal agencies. If sponsors or Federal agencies require that reports of AEs and SAEs be submitted to CHR, these should be provided in aggregate on the sponsors forms. CHR will acknowledge their receipt in writing but will not review them.

CHR Response to Reports of Unanticipated Problems, Unexpected Deaths or Adverse Events That Are More Severe or Occur More Frequently Than Expected

Investigation and review by CHR

¹ AEs and SAEs that occur more frequently than expected can only be detected by the DSMB or Safety Monitor who possess the study randomization code. They, or the PI, are responsible for reporting this finding to CHR within 10 days of being detected.

² The Safety Monitor or DSMB determines the reporting interval (e.g. every 3 months) as part of the safety monitoring plan, which must be reviewed and approved by CHR.

When ORS receives a report of an unanticipated problem, an unexpected death, or an adverse event that is more severe or occurs more frequently than expected, a CHR Co-Chair or a CHR member designated by the Co-Chair will review the report together with all relevant study records. Reports of deaths will be reviewed by a Co-Chair (or designee) within 72 hours; all other reports will be reviewed within 10 days. If additional information is required, this will be requested by the Co-Chair. The Co-Chair will determine whether the problem requires review by the Full Committee. Problems that are determined to not adversely affect the ratio of risks and expected benefits of the study, and are not continuing, will generally be resolved by the Co-Chair (or designee) in discussion with the Principal Investigator. When Full Committee review is required, members will receive a summary of the problem, relevant details and the corrective action recommended by the Co-Chair or designated reviewer. The Full Committee will decide any corrective actions, the Principal Investigator will be notified in writing, and the Committee discussion and decisions will be included in the minutes of the meeting.

Possible decisions and actions by CHR

The CHR may decide to:

- acknowledge the report and take no further action,
- request additional information from the PI, the Safety Monitor or the DSMB,
- request a meeting with the PI or other parties,
- monitor the study for additional similar problems,
- require that the Research Plan and consent documents be revised to include a newly defined expected adverse event;
- require that additional information about the problem be provided to past study subjects,
- require that current subjects be informed about the problem (this is required when the information may affect their willingness to continue to take part in the research);
- require that current subjects be re-consented;
- modify the continuing review schedule;
- monitor consent procedures;
- refer the issue to other organizational entities (e.g., CHR legal counsel or the JHSPH Institutional Official);
- recommend a change in the research protocol or consent form(s),
- temporarily suspend enrollment, or the study treatment or intervention, pending collection of additional information, or
- terminate the study.

Other actions are also possible.

Reporting of CHR Decisions and Actions

Reports of CHR decisions and actions are drafted by the relevant Co-Chair, reviewed by the other Co-Chairs and the Institutional Official, and approved by the Institutional Official. The report to the PI is signed by the relevant Co-Chair. Reports to other JHSPH/JHU officials, Federal agencies or sponsors, and local IRBs are signed by the Institutional Official.

The report will include the following elements:

1. the nature of the event;
2. the findings of CHR, ORS or others who took part in the investigation;
3. a summary of the problems that require corrective action;
4. the corrective actions taken by CHR;
5. the rationale for the actions, and
6. plans for further investigation or follow-up actions, if any.

Copies of the report will be placed in CHR files and be sent to:

1. the Principal investigator,
2. the responsible CHR Co-Chair,
3. the Dean of JHSPH (when appropriate),
4. the Chairperson of the Principal Investigator's department (when appropriate),
5. the highest academic official of any collaborating institution(s) (when appropriate),
6. the Chairperson of the local IRB (when appropriate),
7. the Chairperson of the study DSMB (when appropriate)
8. OHRP with a cover letter signed by the JHSPH Institutional Official,
9. FDA, whenever the study is FDA-regulated, with a cover letter signed by the JHSPH Institutional Official,
10. the Associate Dean for Graduate Education and Research (when appropriate)
11. the Professional Liability Claims Office and the Office of Legal Counsel, if the report raises issues of legal liability or there is a threat or perceived threat of a lawsuit,
12. the study sponsor or the CRO representing the sponsor, if the study is sponsored (when appropriate),
13. the JHSPH Office of Research Administration, if the study is sponsored, and
14. WIRB (when appropriate).

The above reports shall be distributed within 10 days following the decision of CHR on action(s) to resolve the problem.