



# Human Subjects Protection Update Special Communication

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## REVISED REPORTING POLICY:

### Reducing Adverse Event/Unanticipated Problem Reporting & Increasing Reliance on Data and Safety Monitoring Communications with the IRB

In an effort to improve the IRB review process, a significant policy change has been implemented to reduce the number of adverse events that need to be reported to the IRB. This change is coupled with the requirement that PIs provide the IRB with more meaningful information regarding data and safety monitoring activities.

The Committee on Clinical Investigation (CCI) is changing its policy regarding reporting of serious or unanticipated events. The changes bring this policy into alignment with federal regulations in a manner that is consistent with recent guidance from the regulatory agencies. In general, the new policy will reduce the number of individual events that must be reported to the IRB. In conjunction with this change, the CCI will increase its reliance on the investigator-specified data safety and monitoring plan and therefore will require more complete annual updates on the data and safety monitoring plans as part of the continuing review process. It is also important to note that an investigator's responsibility for reporting events to a data and safety monitoring board, sponsor and FDA (if applicable) do not change. The following question and answer document provides the information you will need to implement the changes. The changes become effective immediately.

#### 1. How is Children's Hospital (CH) policy regarding reporting events to the CCI changing?

In the past Children's has required that clinical investigators report all serious adverse or unanticipated events to the IRB regardless of relationship to the protocol. With the new policy, the CCI will accept and review **only** the following:

- **Adverse events that are also unanticipated problems (UP) involving risks to subjects or others (see below)**
- **Unanticipated events that do *not* involve actual harm to subjects or others, but which place research subjects or others at risk of harm that was not previously anticipated.**
- **Any death of a CH study subject thought to be related or possibly related to the research associated interventions.**

These events should be reported within 72 hours of being known

#### 2. Why is CH changing its reporting policy?

CH is changing its policy to be consistent with the federal regulations in a manner that is consistent with recent regulatory guidance. Both the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP) and the FDA have issued recent guidance documents that clearly indicate that IRBs are only required to be promptly notified of unanticipated problems involving risks to subjects or others, as opposed to being informed of *all* adverse events. In fact, most adverse

events do *not* constitute unanticipated problems involving risks to subjects or others, and therefore do not require reporting to the IRB. Additionally some unanticipated problems that require prompt reporting to the IRB do not involve actual harm to subjects or to others. It is also important to note that there are additional categories of events that require reporting that do not involve drugs, devices or research interventions.

### 3. When is the new policy effective?

The policy change is effective immediately. For the next month, the CCI will continue to accept all submitted adverse event reports and those that have been submitted will continue to be processed. However, as of June 1, 2008, reports that do not fit the new criteria will be returned to investigator without action or review.

### 4. What is a Unanticipated Problem (UP) that requires reporting to the CCI?

UP stands for ***Unanticipated Problem involving risks to subjects or others***. According to CH policy, an UP is any incident, experience, or outcome that meets both criteria:

- (1) ***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; and
  - (b) the characteristics of the subject population being studied;

**and**

- (2) ***related or possibly related*** to a subject's participation in the research;

The third criteria for an unanticipated problem is that the event places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized. The investigator is required to report any event that meets the first two criteria of unexpected and related or possibly related. Upon review of the unexpected and related/possibly related events, the IRB will make the final determination as to whether the event places subjects at greater risk of harm than initially anticipated and whether additional actions need to be taken to assure the safety and welfare of research subjects.

It is important to note that an event that does not involve actual physical, psychological, social, or economic harm to a research subject or another person may nevertheless constitute a UP and therefore must be reported. This is the case if the event places subjects or others at increased or different risk of harm than was previously anticipated in the IRB-approved consent document and protocol.

### 5. How can I determine whether an event is ***unexpected?***

An event is unexpected if it occurs in one or more subjects or others participating in a research protocol, and the event's nature, severity, or frequency is **not** consistent with either:

- (1) the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in
  - (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and
  - (b) other relevant sources of information, such as product labeling and package inserts; or

(2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

**6. How can I determine whether an event is related or possibly related to a subject's participation in the research?**

Events may be caused by one or more of the following:

- (1) the procedures involved in the research;
- (2) an underlying disease, disorder, or condition of the subject;
- (3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas events determined to be **solely** caused by (2) or (3) would be considered unrelated to participation in the research.

**7. What is the difference between a UP and an adverse event?**

By definition, a UP is an unanticipated problem, whereas an "adverse event" may be anticipated or unanticipated. Additionally, an UP may involve the increased *risk* of harm—whether or not any actual harm occurred. In order to decide which events or circumstances constitute an UP, it is important to bear in mind the following:

1. **Not all AEs are UPs.** Only a small subset of "adverse events" occurring in FDA regulated clinical trials constitute unanticipated problems and therefore must be reported promptly to the IRB. Many events that are required to be reported to the sponsor or FDA are *not* UPs.
2. **An UP may not be an AE.** It is possible for an event that does *not* involve actual physical, psychological, social, or economic harm to a research subject or another person to nevertheless constitute an UP and therefore must be promptly reported to the IRB. This is the case if the event places subjects or others at increased or different *risk* of harm, regardless of whether actual harm has occurred.

**8. What are some examples of events that are not adverse events, but are UP—and therefore need to be reported?**

- Publication in the literature, safety monitoring report including a Data and Safety Monitoring Report, interim result, or other finding that indicates an unexpected change to the risk/benefit ratio of the research;
- Breach in confidentiality resulting from a disclosure of confidential information or from lost or stolen confidential information, that may involve risk to that individual or others;
- Complaint of a participant or family member that indicates an unanticipated risk;
- Laboratory or medication errors that may involve potential risk to that individual or others;
- Change in FDA labeling because of adverse consequences or withdrawal from marketing of a drug, device, or biologic used in a research protocol;
- Disqualification or suspension of investigators;
- Accidental or unintentional change to the IRB-approved protocol that involves risks or has the potential to recur;
- Deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant

**9. What if a sponsor tells me I must submit Adverse Events even if they are not UPs?**

- A. Please provide the sponsor with a copy of the letter we have prepared and placed on our website explaining our policy. You may find this letter on our website under the forms section .

- B. If they are unwilling to accept this as CH policy, then contact the Clinical Investigation office in order to discuss how we can accommodate their request for submission to the IRB. If this is to occur the CCI office will require documentation that the PI has reviewed the events and determined that they do not constitute UPs (otherwise they would be reported). The CCI will provide the investigator with documentation that the reports were submitted, but were not reviewed because according to the Investigator they did not constitute UPs.

**10. Will this new policy change data and safety monitoring plans and the need for DSMB reports.**

Yes. In order to eliminate excessive reporting to the IRB, the IRB will require assurance that there is an appropriate mechanism to monitor the research on an ongoing basis as part of the protocol application. The IRB will not approve greater than minimal risk research without a complete data and safety monitoring plan. They will also require evidence that data and safety monitoring occurs on an ongoing basis. Many events that no longer need to be reported to the IRB, will still need to be reported to a DSMB, a sponsor or the FDA, through the mechanism specified in the protocol's data and safety monitoring plan. Since individuals or committee's assigned responsibility for data and safety monitoring are experts in the area of study, they are in the best position to monitor all the events. It is expected that data safety monitoring reports will be provided to the IRB. New protocol submissions will need to include, a description of the plan and how often data and adverse reports will be reviewed. Investigators will be expected to submit evidence of this review and any associated reports as part of the continuing review submission.

**11. What happens if the Principal Investigator does not agree with the Sponsor's assessment of the relationship between the study drug and the UPs?**

If either the PI or the Sponsor considers the event to be an UP, then a report should be filed. The contrary opinions can be elaborated in the report.

**12. Does this mean I do not need to worry or track about events that may be serious and expected?**

No. Investigators are always required to record or track events thought to be serious and related as part of your research protocol. You are still required to report these events to the sponsor and any data and safety monitoring entirety. In addition the continuing review reports will ask whether based on these reports the risk profile has changed for the protocol and to summarize these events as part of the continuing review. The change in policy concerns only what needs to be submitted to the IRB and does not impact what investigators need to record, document as part of their research records.

**13. Do I still need to submit an Unanticipated Adverse Device Effect Report if the sponsor has already sent one to the IRB?**

Since device regulations have some specific reporting requirements, there are some additional requirements for research involving investigational devices. Even though a sponsor is required to report an unanticipated adverse device effect under 812.150(b)1 to the FDA, all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect, the Principal Investigator's assessment of the event is necessary to determine if any changes to the approved study should be made as a result of the report. The Investigator should use the Unanticipated Event Reporting Form, indicating whether the report constitutes an UP, or submitting it under the "other" category.

**14. Examples: Please review the following examples which help clarify**

**how the above mentioned principles apply to the revised reporting requirements.**

**Examples of unanticipated problems that are not adverse events are therefore need to be reported to the IRB:**

(a) An investigator conducting behavioral research collects individually identifiable sensitive information about illicit drug use and other illegal behaviors by surveying high school students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's office. This is an unanticipated problem that must be reported because the incident was (a) unexpected (i.e., the consent document and IRB-approved protocol or NPSF did not anticipate the theft as an expected risk of participation); and (b) the event was related to participation in the research.

(b) As a result of a processing error by a pharmacy technician, a subject enrolled in a multicenter clinical trial receives a dose of an experimental agent that is two times higher than the dose indicated in the IRB-approved protocol. While the dosing error increased the risk of toxic manifestations of the experimental agent, the subject experienced no detectable harm or adverse effect after an appropriate period of careful observation. Nevertheless, this constitutes an unanticipated problem for the institution where the dosing error occurred that must be reported to the IRB, because the incident was (a) unexpected; and (b) related to participation in the research.

(c) Subjects with hemophilia are enrolled in a phase 2 clinical trial evaluating an investigational biologic product derived from human sera. After several subjects are enrolled and receive the investigational product, a study audit reveals that the investigational product administered to subjects was obtained from donors who were not appropriately screened and tested for several potential viral contaminants, including the human immunodeficiency virus and the hepatitis B virus. This constitutes an unanticipated problem that must be reported because the incident was (a) unexpected; and (b) related to participation in the research.

The events described in the above examples were unexpected in nature, related to participation in the research. Once reported, the IRB will then determine if the event placed the subject or others at greater risk of physical, psychological or social harm and whether any additional actions or reporting needs to occur. Unanticipated problems may warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects. In addition, the third example may have presented unanticipated risks to others (e.g., the sexual partners of the subjects) in addition to the subjects. In each of these examples, while these events may not have caused any detectable harm or adverse effect to subjects or others, they nevertheless represent unanticipated problems and should be promptly reported to the CCI.

**Examples of adverse events that are not UPs—and therefore do not need to be reported to the IRB:**

(d) A subject enrolled in a phase III, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers. The IRB-approved protocol and informed consent document for the study indicated that there was a 10% chance of developing mild to moderate gastritis and a 2% chance of developing gastric ulcers for subjects assigned to the active investigational agent. The investigator concludes that the subject's gastric ulcers resulted from the research intervention and withdraws the subject

from the study. A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers – in terms of nature, severity, and frequency – was expected.

(e) A subject is enrolled in a phase III, randomized clinical trial evaluating the relative safety and efficacy of vascular stent placement versus carotid endarterectomy for the treatment of patients with severe carotid artery stenosis and recent transient ischemic attacks. The patient is assigned to the stent placement study group and undergoes stent placement in the right carotid artery. Immediately following the procedure, the patient suffers a severe ischemic stroke resulting in complete left-sided paralysis. The IRB-approved protocol and informed consent document for the study indicated that there was a chance of stroke for both study groups. To date, 25 subjects have been enrolled in the clinical trial, and 2 have suffered a stroke shortly after undergoing the study intervention, including the current subject. The DSMB responsible for monitoring the study concludes that the subject's stroke resulted from the research intervention. This example is not an unanticipated problem because the occurrence of stroke was expected and the frequency at which strokes were occurring in subjects enrolled so far was at the expected level.

(f) An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurements, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describe claustrophobic reactions as one of the risks of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research. This example is not an unanticipated problem because the occurrence of the claustrophobic reactions – in terms of nature, severity, and frequency – was expected.

**Examples of adverse events that are UPs—and therefore require reporting to the IRB:**

(h) A subject with chronic gastroesophageal reflux disease enrolls in a randomized, placebo-controlled, double-blind, phase 3 clinical trial evaluating a new investigational agent that blocks acid release in the stomach. Two weeks after being randomized and started on the study intervention the subject develops acute kidney failure as evidenced by an increase in serum creatinine from 1.0 mg/dl pre-randomization to 5.0 mg/dl. The known risk profile of the investigational agent does not include renal toxicity, and the IRB-approved protocol and informed consent document for the study does not identify kidney damage as a risk of the research. Evaluation of the subject reveals no other obvious cause for acute renal failure. The investigator concludes that the episode of acute renal failure probably was due to the investigational agent. This is an example of an unanticipated problem that must be reported because the subject's acute renal failure was (a) unexpected in nature and (b) related to participation in the research.

(i) A behavioral researcher conducts a study in college students that involves completion of a detailed survey asking questions about early childhood experiences. The research was judged to involve no more than minimal risk and was approved by the IRB chairperson under an expedited review procedure. During the completion of the survey, one student subject has a transient psychological reaction manifested by intense sadness and depressed mood that resolved without intervention after a few hours. The protocol and informed consent document for the research did not describe any risk of such negative psychological reactions. Upon further evaluation, the investigator determines that the subject's negative psychological reaction resulted from survey questions that triggered repressed memories of physical abuse as a child. The investigator had not expected that such

reactions would be triggered by the survey questions. This is an example of an unanticipated problem that must be reported in the context of social and behavioral research because, although not serious, the adverse event was (a) unexpected and (b) related to participation in the research.

(j) The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The IRB-approved protocol and informed consent document for the study identifies mild liver injury as a risk of the research. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study agent. This is an example of an unanticipated problem that must be reported because although the risk of mild liver injury was foreseen, severe liver injury resulting in hepatic failure was (a) unexpected in severity and (b) possibly related to participation in the research.

In all these situations the IRB reviews the event to determine if subjects or others are placed subjects at a greater risk of physical, psychological or emotional harm than was previously known or recognized . They will also determine if additional actions and reporting is necessary.

**Examples of research subject deaths that do and do not need to be reported to the IRB:**

(k) A subject participating in a phase III, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new investigational therapeutic agent combined with the current standard therapeutic agent, versus placebo combined with the current standard therapeutic agent regimen, for the management of leukemia develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies. Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infection is a known complication of the therapeutic regimens being tested in this clinical trial and these risks are described in the IRB-approved protocol and informed consent document. The investigators conclude that the subject's infection and death are directly related to the research interventions. This example although it is not an unanticipated problem because the occurrence of severe infections and death – in terms of nature, severity, and frequency was included in the consent would be a reportable death to the IRB

(l)A subject is participating in a research protocol that involves two forms of behavioral interventions. The investigator is informed the subject was a passenger in a car and was killed in an automobile accident. In this case the death was unrelated to participation in the study.

(m) An investigator performs prospective medical chart reviews to collect medical data on premature infants in a neonatal intensive care unit (NICU) for a research registry. An infant, about whom the investigator is collecting medical data for the registry, dies as the result of an infection that commonly occurs in the NICU setting. This example is not an unanticipated problem because the death of the subject is not related to participation in the research, but is most likely related to the infant's underlying medical condition

**15. What if I have questions regarding this policy and require assistance?**

If there are any questions or concerns or you need assistance interpreting this new policy, please call the protocol administrator assigned to your department at 57052.

Reference Documents

OHRPs guidance document

*Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*

U.S. Department of Health and Human Services: Office for Human Research Protections. (January 15, 2007) <http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>.

FDA guidance document

*Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting — Improving Human Subject Protection (Draft Guidance)*

U.S. Department of Health and Human Services: Food and Drug Administration  
April 2007 <http://www.fda.gov/cber/gdlns/advreport.pdf>