

Instructions for the IRB Reportable Event Prompt Reporting Form

For IRB protocols still on paper due to being approved under the older regulation or prior to implementation of eProtocol, the paper version of this form can be downloaded from the IRB website and submitted to the IRB via email at ORP@depaul.edu. If the IRB protocol was submitted and approved through the online eProtocol system, the Reportable Event Prompt Reporting Form must be submitted through the online eProtocol system.

Background

Federal regulations under 45 CFR 46.103 (a) and (b) 5 require that institutions have written procedures for reporting the following types of incidents promptly to the IRB and the federal Office for Human Research Protections (OHRP):

- a. Any unanticipated problems involving risks to subjects or others;
- b. Any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and
- c. Any suspension or termination of IRB approval.

The reporting requirements apply to all nonexempt human subject research which is conducted or supported by HHS, conducted or supported by any non-HHS federal department or agency that has adopted the Common Rule and is covered by a Federalwide Assurance (FWA) determined to be appropriate for such research, or covered by an FWA, regardless of funding source.

Federal regulations do not define ‘promptly’, but for serious events, it may mean reporting to OHRP in days. For less serious incidents, a few weeks may be sufficient. The IRB may want to submit an initial report of an incident, followed by a final report at a later date. DePaul policy requests a report within 5 working days of the event or learning of the event.

In order to ensure that the DePaul IRB is able to meet the reporting requirements for events, we must have a process for researchers to report events to the IRB for review. The reporting of events also plays a key role in minimizing risks to and protecting research subjects. In order for the IRB to approve research, the IRB must determine, among other things, that:

- Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever possible, by using procedures already being performed on the subject for diagnosis or treatment purposes.
- Risks to subjects are reasonable in relation to anticipated benefits, if any, to the subjects, and the importance of the knowledge gained that may reasonably be expected to result.
- When, appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

Receiving reports of events, provides the IRB with the information it needs to ensure that the risks to subjects remain minimized by having adequate protections in place for the subjects. The IRB's main concern is protecting the research subjects. However, the IRB also protects the institution by ensuring we follow the requirements for reporting to federal agencies.

Definitions

Adverse event: 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.

- Adverse events may be physical or psychological harms. They occur most often in the context of biomedical research, but can occur in the context of social/behavioral/educational research.

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events*.

Possibly related to the research: There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research.

Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. requires inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem involving risks to subjects or others (UPIRSO): Any incident, experience, or outcome that meets all of the following 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;
2. related or possibly related to a subject's participation in the research; and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

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.

Unexpected adverse event: Any adverse event occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which 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.

Instructions for Submitting Events for IRB Review

The Reportable Event Prompt Reporting Form should be used to report incidents to the IRB for review. However, not everything that happens in your research needs to be reported to the IRB. The type of events that do not require prompt reporting to the IRB include:

- Local adverse events or problems that are expected based upon the protocol or consent risk sections or that are not associated with a greater risk of harm to the subject or others than was previously known based upon the information provided in the protocol application or consent.
- External adverse event or problem lacking documentation that an analysis has occurred which determined the event/problem is unanticipated, related or possibly related and associated with a greater risk of harm than was previously known.

The types of events that should be promptly reported with this form include:

- Unanticipated adverse events and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

- New information that unexpectedly alters the risk or benefits to the research subjects
- Subject death
- Significant protocol deviations
- Significant protocol violations
- Serious adverse events
- Noncompliance
- Subject complaints that cannot be handled by the PI
- Any other events that require prompt reporting according to DePaul policy, i.e., breaches in confidentiality

In general, events that meet all three criteria for being a UPIRSO must be reported to the IRB: 1) unexpected; 2) related or possibly related to the research; 3) puts subjects or others at risk of harm. Only a small number of adverse events will meet the three criteria for a UPIRSO and require reporting to the IRB. Also, there are some events that are unanticipated problems, but which are not adverse events, as an adverse event is more in line with biomedical FDA-regulated research.

OHRP guidance indicates that there are adverse events that are not unanticipated problems, there are unanticipated problems that are not adverse events, and then there are adverse events that are unanticipated problems. See the Venn diagram at: <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q3>.

The diagram indicates that a small proportion of events that need to be reported promptly. However, as it may be difficult determining relation and whether an event is unexpected, there is no harm in reporting an event to the IRB to obtain their determination on the event.

It may be difficult to determine whether a particular incident or outcome is unexpected and whether it is related or possibly related to participating in the research, but it is expected that incidents that meet all three of the criteria for a UPIRSO may require changes to the research protocol and/or consent process or other corrective action plans to protect the safety, welfare, or rights of the human subjects or others.

Adverse events may be caused by: 1) the procedures involved in the research; 2) an underlying disease, disorder or condition of the subject; or 3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject. Events determined to be caused by (1) would be considered related to the research, while events caused by (2) or (3) would be considered to be unrelated to the research. Generally, events are rated as definitely related, possibly related, or not related. Any event that is definitely or possibly related to the research must be reported to the IRB.

The first step in determining whether an adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized is to ask whether the adverse event meets the criteria for a serious adverse event (see the definition above). Adverse events that are unexpected, related or possibly related, and serious are the most important subset

of events that should be reported to the IRB because they suggest the research is placing subjects at risk and the research may require revisions to prevent this risk.

Adverse events that are unexpected and related or possibly related to the research, but not serious would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. These types of events should be reported promptly to the IRB.

Some events that are unanticipated problems, but are not related to adverse events, should be reported promptly to the IRB. OHRP guidance provides some examples of these types of events in Appendix B to their guidance: <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#AB>

In the form:

Complete the date you completed the form. Then complete the requested PI information. If you are a student and have a Faculty Sponsor, complete the Faculty Sponsor information.

I: Indicate the protocol number, project title, and the current level of review.

There are instructions for the types of events to report and what types of events do not require prompt reporting.

Item 1: Type of Report: Item (a) asks whether this is an initial report (the first time you are telling the IRB about the incident) or a follow-up report. A follow-up report might be needed if you needed to submit a report in the required 5 working day time frame, but did not have all of the necessary information. You would then provide the final information in a follow-up report. If this is a follow-up report, we would ask for the date of the initial report, just to be sure we match up the two reports correctly, particularly if more than one event was submitted within a similar time-frame.

Item (b) asks whether this is an internal report. Most events will be internal reports, but with the increase in IRB reliance agreements, there may be more external reports submitted. Item c asks if this is an external report (one that happened at a non DePaul collaborating site, but which may impact DePaul subjects in some way).

Item II: Study Related Information: Item (a) asks for how many subjects are enrolled currently in the research. The IRB would like this information to get a sense of how far a researcher may be from the approved number of subjects and how many subjects may be impacted by the event.

Item (b) asks for the status of the research, which also helps the IRB determine the overall impact of the event on the research subject and this information may impact the decided upon action plan.

Item III. Type of Event: This item includes check boxes for the most common types of events which require reporting to the IRB. The form is meant to be used to report all types of possible events, including instances of non-compliance. Sometimes, an event may actually fit into more than one category, so you may check more than one box. For example, an event might be an unanticipated problem and involve unintentional non-compliance. Therefore, two boxes should be checked. There is an 'other' category for events that do not fit into the common categories of events. For serious adverse events, the various types of serious adverse events defined in regulations and guidance are included in the list.

Item IV: A detailed description of the event. For this item there are bullet points that indicate all the information the IRB needs about the event. The three most important items are the assessments of unexpectedness, relation to the research, and the risks to the subjects or others. Information is provided above in the definition section of these instruction to aid in making these determinations. We need all this information to decide about the actions to take, should further actions be needed, and when we report the event to OHRP, if that is necessary.

Item V: Actions Taken. Item (a) asks for information about the actions you have taken this far in response to the event. Sometimes, these may be all the actions needed, and other times, these actions may be limited to initial actions to eliminate immediate harm as part of a preliminary report. Other times, the IRB may determine that additional corrective action are needed, but before the IRB can determine that, they need to fully understand what the researcher has already done.

Item (b) asks about any changes you may make to your research to address the event. For example, sometimes it is necessary to revise your protocol to include enhanced safety measures, additional protections in place for confidentiality of the data (due to a potential breach of confidentiality), or to alter your research procedures. This part of the form would ask that you outline or summarize the changes. It is expected that the actual changes will be submitted as an amendment to your approved protocol. The amendment may be submitted at the same time as the event report or shortly afterwards.

Item VI: Outcome: There are check boxes for the likely outcome for the individual subject or group of subjects involved in this event. Check the box that is appropriate. If the specific outcome is not noted, then check 'other' and explain the outcome. If this does not apply, indicate NA.

Item VII: This item asks if this problem has occurred before in this research protocol. This information helps the IRB determine whether initial corrective action plans may need to be updated or supplemented, if they have not prevented the problem from reoccurring.

Item VIII: This item asks if the risks of the research or the risk/benefit ratio has changed. It is important for the IRB to understand if there are new risks, but also, if with the new risks, the risks now outweigh the benefits. One of the IRB approval criteria under the regulations indicates that in order to approve the research, the IRB must determine "Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." Therefore, if there are new risks to the research, the IRB must

make a new determination as to whether the risks of the research are still acceptable in relation to the known or potential benefits.

Item IX: Informed consent process. Item (a) asks whether the problem or issue is currently indicated in the currently approved consent document, parent/legal guardian permission, and/or assent. This is most applicable when the event is about a new or heightened risk. If the risk is not listed and should now be or the risk section needs to be updated, the form goes on to ask for more information. Some events are not related directly to the risks listed in the consent document, parent/legal guardian permission, and/or assent, so the best response to this item might be NA.

Item i, asks for how the documents will be revised to reflect the new risk(s). This should be completed with a summary of the specific language that will be added.

Item (b) asks whether past subjects, the currently enrolled subjects or future subjects will be told about the issue. And then (i) asks the researcher to identify which group of subjects will be informed. Most of the time, the issue would only impact the subjects currently enrolled or future subjects. However, there are times where you might need to go back to past subjects and inform them of a problem, such as a breach of confidentiality or some long-term latent effect of an intervention or treatment that was not previously known.

Item (c) asks for the researcher to outline their plan for providing the information to the past, current, or future subjects. The plan might be a consent addendum, revised consent, an information letter, or a verbal script. The plan and new/revised documents would be part of an amendment to the protocol and the corrective action plan.