



Human Research Protection Office Guide: Managing and Reporting Incidents

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This guide in context

The CDC Human Research Protection Office (HRPO) has issued guidance and forms for submitting and tracking human research protocols. These documents cover key features of CDC's responsibilities for reviewing CDC's research activities involving human subjects and for tracking CDC's research partners. All guidance documents and forms are intended for use throughout CDC. NCHS users should consult the NCHS human subjects contact (HSC) or the Research Ethics Review Board (ERB) for NCHS-specific procedures; NIOSH users should consult the NIOSH HSC or the Human Subjects Review Board (HSRB) for NIOSH-specific procedures. See the *HRPO Guide: Overview* for general information and a complete list of forms and guides.

Managing incidents and adverse events

- 0.1254 Incident Report
- 0.1254S Supplemental Report on Adverse Events

This guide describes the responsibilities and procedures for managing and tracking incidents in human subjects research conducted by CDC. The following kinds of incidents must be reported to the CDC IRB:

- Unanticipated problems involving risks to subjects or others, including the following kinds of adverse events:
 - Serious, unexpected, and related or possibly related to the research procedures
 - Serious, expected, but occurring at a significantly higher frequency or severity than expected
 - Other unexpected adverse events, regardless of severity, that may alter the analysis of the risk versus potential benefit of the research and warrant consideration of substantive changes in the research protocol or consent process
- Serious or continuing noncompliance
- Suspension or termination by an IRB (for reasons other than expiration)
- Other incidents as specified in the protocol or requested by the IRB

CDC form 0.1254 is required for reporting these incidents to the CDC IRB. Companion form 0.1254S may be used for reporting details of adverse events. Form 0.1254S is intended primarily for supplemental information on adverse events that are also unanticipated problems involving risks to subjects or other, but may be used for other adverse events. When the information on 0.1254S is required, it may be reported in any printed format that contains elements necessary to characterize adverse events.

All forms are supplied as Microsoft Word documents with 3 kinds of fields for entering information.

Free text fields are displayed with gray underscore. These fields allow the user to type any text into them, but some of these fields have limits on the number or type of characters allowed.

A *checkbox* may be marked or unmarked by clicking inside the box with the cursor.

A selection may be made from a *dropdown list* by clicking on the field and selecting one item from the list of choices.

Responsibilities and definitions

Form 0.1254 covers reporting requirements as found in US federal regulations for the protection of human subjects¹. These regulations require promptly reporting unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspensions or terminations by the IRB. The regulations do not, however, define these terms. Therefore, CDC has adopted the definitions in this document.

Four ethical responsibilities guide the overall process for responding to incidents:

1. Recognize when something happens that could affect research risk to subjects or others.
2. Manage the immediate harm or risk.
3. Be accountable for how the harm or risk is managed.
4. Manage further risk.

1 Recognizing incidents

The first responsibility in responding to an incident is to recognize it. Recognition follows in part by properly applying the definitions in this section. Each protocol should characterize which incidents must be reported promptly, in detail appropriate to the level of anticipated risk.

1.1 Unanticipated problems involving risks to subjects or others

Risk is potential harm, expressed in terms of the probability and magnitude of harm. OHRP considers unanticipated problems, in general, to include those events that are not expected given the nature of the research procedures and the subject population being studied and that suggest that the research places subjects or others at greater potential for research-related harm or discomfort than was previously known or recognized.

Under CDC procedures, an incident is an unanticipated problem involving risks to subjects or others if it meets one or more of the following 6 criteria:

1. The problem occurs any time during or after a research study, at any site participating in the research study, which in the opinion of the principal investigator (PI) meets these three additional criteria:
 - a. One or more participants or others experienced harm or were placed at increased risk.
 - b. The specificity and severity of the event were not accurately reflected in material reviewed by the IRB at time of approval, such as material presented to participants, investigator's brochure, and package insert.

¹ See 45 CFR 46.103(b)(5) for research that is conducted or supported by HHS and 21 CFR 56.108(b) for clinical investigations that are subject to FDA regulations.

- c. The problem could have been caused by research procedures. More precisely, the PI was unable to document a more probable cause for the event than research procedures.
2. A participant expresses a complaint that indicates unexpected risks.
3. A valid report (such as interim findings, safety monitoring report, or publication in the literature) indicates an increase in severity or frequency of expected risks, or a decrease in potential benefits, of research procedures.
4. For a drug, biologic, or device used in the protocol, the article is withdrawn from marketing or the regulatory label changes to reflect an increase in severity or frequency of expected risks or decrease in potential benefits.
5. An accidental or unintentional change to the IRB-approved protocol places one or more participants at increased risk.
6. An intentional change to protocol is taken without prior IRB review to eliminate an apparent immediate hazard to a participant.

Many unanticipated problems—such as equipment failure, delays in conduct of a study, or loss of funding—are not reportable in this category if they do not involve risks to subjects or others.

Some, but not all, adverse events fall into this category. Under regulations for the protection of human research subjects, adverse events must generally be reported promptly to the IRB only if they qualify as unanticipated problems involving risks to subjects or others. These are described further in section 1.4 on page 4. Other adverse events that do not fall into this category may be reportable if specified in the protocol or requested by a governing IRB.

Many unanticipated problems involving risks to subjects or others are not adverse events as defined below. Possible examples include breach of confidentiality, inclusion of ineligible subjects, and giving subjects incorrect information or information that upsets them.

1.2 Serious or continuing noncompliance

CDC defines *noncompliance* as failure by investigators, research staff, IRB members, or IRB staff to follow regulations for human research protections (45 CFR part 46; 21 CFR parts 50 and 56), the terms of their Federalwide Assurance to the Office for Human Research Protections (OHRP), or requirements of the governing IRB(s).

CDC defines *serious noncompliance* as noncompliance that results in increased risk to participants or reflects a failure to apply substantial portions of governing regulations. Examples of serious regulatory noncompliance include, without limitation, the following:

- Conducting nonresearch that should have been deemed research
- Conducting nonexempt research without IRB review and approval, for example, by incorrectly deeming the research exempt
- Beginning enrollment of subjects without proper IRB approval
- Approving research by expedited review when approval by a convened IRB is required
- Implementing substantive changes in approved research without prior IRB review and approval
- Including any prisoners, pregnant women, or children without proper review and documented approval
- Failing to send required reports promptly to the governing IRB(s) or regulatory agencies.

CDC defines *continuing noncompliance* as repeated occurrences of noncompliance. This category applies especially, though not exclusively, to noncompliance that recurs after it has been identified. These incidents of noncompliance may or may not also reflect serious noncompliance.

These regulatory categories appear to have been worded in part to avoid requiring that minor infractions be reported promptly. Infractions that do not constitute serious or continuing noncompliance should still be brought to the attention of the IRB at least upon continuing review. For example, if the protocol states that subjects will initial every page of the consent document, occasional failure to do so would not constitute serious or continuing noncompliance, as this practice goes beyond the requirements of the regulation and the CDC IRB.

1.3 Suspension, termination, and related terms

At CDC, *suspension* is defined as the temporary cessation of both research-related intervention or interaction with participants and collection or use of identifiable private research information. Partial suspension halts some but not all such activities, for example when enrollment is stopped but follow-up continues with enrolled subjects. “Administrative holds” by the IRB are considered reportable suspensions. A suspension by the IRB must be reported promptly unless the suspension results from expiration of IRB approval.

CDC defines *termination* as the permanent cessation of both research-related intervention or interaction with participants and collection or use of identifiable private research information; the term is usually applied to cessation before study objectives have been met. *Withdrawal* is defined as permanently halting a research study after submission for IRB review but before human subjects become involved, whether or not the study has been reviewed by an IRB. *Closure* is an action taken when study objectives have been met, proactively and permanently ending both research-related intervention or interaction with participants and collection and use of identifiable private research information.

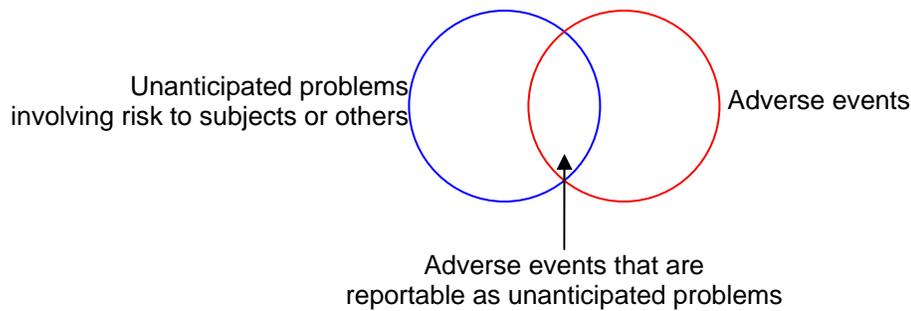
A termination by the IRB must be reported promptly unless either (a) the termination results from expiration of IRB approval or (b) the termination represents withdrawal or closure of a research protocol for reasons other than research risks. A withdrawal would not be reportable, for example, if the study were halted due to a lack of funds. A withdrawal would be reportable if it occurred because new information about risks indicated that the study would no longer be ethical to conduct as designed.

A suspension or termination by anyone other than the IRB should be reported to the IRB, but it does not need to be reported to regulators unless the suspension or termination occurs because of unanticipated problems involving risks to subjects or others or serious or continuing noncompliance.

1.4 Adverse events

As explained above, adverse events are generally reportable to the IRB only if they qualify as unanticipated problems involving risks to subjects or others. OHRP has issued draft guidance on the relationship between and reporting requirements for adverse events and unanticipated problems involving risks to subjects or others². In this section, key terms are defined for the analysis of adverse events. Then OHRP’s guidance is described, including a delineation of those adverse events that should be reported promptly as unanticipated problems.

² See OHRP’s *Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others*, at www.hhs.gov/ohrp/requests/aerg.html.



The protocol or IRB may require prompt or periodic reporting of additional categories of adverse events. Furthermore, adverse events in studies of unapproved drugs, biologics, or devices may need to be reported to a sponsor or regulatory agency under regulations governing pre-marketing investigations of test articles³; these instructions do not address pre-market reporting requirements (but see page 7).

Adverse event

The International Conference on Harmonization (ICH) defines adverse event⁴ narrowly for clinical investigations, especially to accommodate pre-approval articles under development. To allow for other kinds of interventions, CDC uses an expanded definition of *adverse event*: Any untoward health-related occurrence (a) in a subject administered a health-research intervention and (b) which does not necessarily have to have a causal relationship with this intervention. An adverse event can be any unfavorable and unintended sign, symptom, or condition temporally associated with the administration of the health-research intervention, whether or not considered related to the intervention. This also includes unfavorable deviations from baseline health.

Seriousness and severity

Following the ICH, an adverse event is *serious* if the event

- results in death,
- is life-threatening (at the time of the event),
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, *or*
- is a congenital anomaly or birth defect.

Some adverse events may also be considered serious if they jeopardize the subject or require intervention to prevent one of the other outcomes listed.

³ See FDA regulations at 21 CFR parts 312 and 812:

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=312;

www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812.

⁴ Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. International Conference on Harmonization, §II.A.1; www.ich.org.

Severity is graded in terms of interference with usual social and functional activities:

- mild: no or minimal interference with usual social and functional activities
- moderate: greater than minimal interference with usual social and functional activities
- severe: inability to perform usual social and functional activities
- life-threatening: inability to perform basic self-care functions; or medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
- death

Severity is often standardized in tables, such as toxicity tables published by the World Health Organization or the National Institutes of Health.

The ICH observes that “serious” and “severe” are not synonymous. Seriousness is based on outcomes and their impact on social and functional activities, but severity describes the graded level of intensity. Thus, a severe event may or may not also be a serious adverse event. Investigators may, however, explicitly deem some severe events to be considered serious, especially if they require intervention to prevent the adverse event from becoming serious. For example, in a particular protocol liver toxicity may be an expected side effect that could escalate rapidly. For that protocol, occurrences of severe or even moderate liver toxicity may be considered serious. Seriousness may be documented through a combination of graded and outcome-oriented criteria, such as laboratory values and discrete clinical outcomes.

Expectedness

An adverse event is *unexpected* if the event is previously unobserved or undocumented in humans under the research intervention (or one substantially similar), the nature or severity of the event is not consistent with information in the relevant source documents (e.g., investigator’s brochure, package insert, or non-reportable events [NRE] list), or the event is observed with higher frequency than previously observed or documented. Expectedness does not include results that may be predicted from in vitro, animal, or other pharmacological models.

Relation, causality, or attribution

The relation between an adverse event and research intervention may be characterized by grades of likelihood:

- definitely: direct association with research intervention
- probably: more likely explained by research intervention than any other cause
- possibly: research intervention and other cause are explained equally well
- probably not: more likely explained by another cause than by research intervention
- not: clearly explained by another, documented cause

Adverse events requiring prompt reporting to IRBs

OHRP considers an adverse event to qualify as an unanticipated problem, therefore requiring prompt reporting, if it falls into one of the following categories:

- Adverse events that are serious, unexpected, and related or possibly related to participation in the research.
- Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.
- Other unexpected adverse events, regardless of severity, that may alter the IRB’s analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or consent process.

Other adverse events that are not unanticipated problems may be reportable if specified in the protocol or requested by a governing IRB.

Other considerations pertaining to adverse events

When specific adverse events or classes of adverse events are foreseeable or must be reported in different ways to different entities, the protocol should describe in detail how adverse events will be managed (see also section 2), categorized, documented, and reported.

How will foreseeable adverse events be managed in real time? For example, if a specific toxicity might be expected, how will it be treated? Is there a substitute intervention? Such immediate responses should be thought out in advance and specified to the extent possible.

Consider this example of categorizing, documenting, and reporting adverse events: “All adverse events that meet at least two of these criteria will be documented: serious, unexpected, *or* possibly related to the research intervention. Only those that are serious, unexpected, *and* possibly related to the research intervention will be reported promptly to the IRB as unanticipated problems involving risks to subjects or others. All documented adverse events, whether reported promptly or not, will be reported in summary form to the safety review group every three months and to the IRB on continuing review.”

2 Managing immediate harm or risk

The second responsibility in responding to an incident is to manage the immediate harm or risk according to the nature of the harm or risk. Each protocol should describe how foreseeable immediate harm or risk will be handled.

If there was actual harm, then one should manage the harm according to the protocol or responsible practice. This may entail removing the immediate source of harm. If it is necessary to deviate from the protocol, such deviations must be documented and reported. Finally, the harmed participant(s) should be compensated as indicated in the informed consent.

If there was no actual harm but there is an increase in risk, then one should mitigate the immediate source of the risk and seek further direction, such as from the sponsor, governing IRB(s), or collaborators.

When managing immediate harm or risk, avoid taking irreversible action in anticipation of action by a sponsor or an IRB. For example, do not destroy data, specimens, or linkage before IRB review. Rather, consider holding affected items in escrow, pending review. Also consider regulations about retention of records in human research.

3 Being accountable for how the harm or risk is managed

The third responsibility in responding to an incident is to be accountable for how harm or risk is managed. This responsibility is met through proper documentation and reporting. Each protocol should describe how incidents will be documented, reported, and tracked.

Incidents should be well documented in anticipation of reporting them to the IRB and to regulatory agencies. CDC forms include information that is generally sought by OHRP⁵ and some additional information of use to the IRB. Form 0.1254 focuses on those incidents that human research regulations require to be reported—unanticipated problems involving risks to subjects or others,

⁵ See OHRP’s Guidance on Reporting Incidents to OHRP, 2005-05-27, at www.hhs.gov/ohrp/policy/incidreport_ohrp.html.

serious or continuing noncompliance, and suspension or termination by the IRB—as well as additional incidents as specified in the protocol or requested by the IRB. Form 0.1254S provides an optional format for additional information about adverse events, especially those that are reportable as unanticipated problems involving risks to subjects or others.

Many incidents that do not require prompt reporting to the IRB must nevertheless be well documented and reported periodically. For example, serious but expected adverse events should be summarized periodically for review by safety monitors or the IRB to determine if any events occur more frequently than expected. This additional reporting should be described in the protocol. Further reporting may also be required by the FDA or by the sponsor and should be submitted according to their requirements for formatting and timeliness. The IRB should be informed of these reports periodically, such as upon continuing review.

4 Managing further risk

The fourth responsibility in responding to an incident is to manage further risk, both to currently affected subjects and those yet to be enrolled. This may entail changing the conduct of the study and the roles of study staff. These changes should be reviewed by an IRB before being implemented, unless necessary to remove an apparent immediate hazard to a participant. Each protocol should briefly describe how investigators will approach handle changes or other actions in response to incidents.

Sample actions to address unanticipated problems involving risks to subjects or others may include without limitation: suspension of subject enrollment, suspension of research interventions and interactions in already enrolled subjects, revising the protocol, revising the informed consent document, informing previously enrolled subjects, and increasing monitoring of subjects.

Sample actions to address serious or continuing noncompliance may include without limitation: educating the offending investigator or other party, suspending the protocol, suspending the offending investigator or other party, and conducting random audits of study sites.

Sample actions to address suspension or termination may include without limitation: investigating alleged noncompliance, educating staff, and requiring monitoring of the investigator or the research project.

Procedures for managing and reporting incidents

1 Scope of CDC procedures

The procedures described in this document apply to all CDC-conducted research involving human participants, that is, where CDC employees or agents obtain data about living individuals through intervention or interaction with them or obtain identifiable private information about living individuals. These procedures apply whether the activity is under review by a CDC IRB or by another IRB upon whom CDC relies.

2 Incidents that must be reported promptly

CDC staff may learn about reportable incidents through active reporting from a study site, active solicitation by CDC, or passive discovery by CDC. An incident in one or more of the following four categories must be reported promptly to the CDC IRB (or relied-upon IRB, if applicable):

- Unanticipated problems involving risks to subjects or others
- Serious or continuing noncompliance

- Suspension or termination by the IRB
- Other incident that is reportable to IRB per protocol or per IRB

As described in the next section, “promptly” means informally within 2 working days of CDC staff awareness of the incident and formally within 2 weeks of CDC staff awareness of the incident. If an incident is deemed reportable to a regulatory agency, that report must be submitted by HRPO within 1 week of IRB disposition.

Incidents in the fourth category (per protocol or per IRB) must be reported promptly to the IRB but generally do not need to be relayed to regulatory agencies under human research protection regulations. For example, an IRB may require prompt reporting of all deaths, whether related to the research intervention or not. Unrelated deaths would then be reported promptly to the IRB, but unless they are deemed unanticipated problems involving risks to subject or others, they would not need to be reported to regulatory agencies.

3 Procedures arranged chronologically

The following procedures are listed approximately chronologically. These procedures emphasize promptness over completeness. That is, available information must be reported as quickly as possible, with later follow-up on incomplete information as needed.

1. The incident happens and is managed by study staff at the site of occurrence.
2. CDC program staff (generally the CDC PI) become aware of the incident.
3. CDC program staff sends an e-mail message to HRPO within 2 working days of CDC awareness of reportable incident. If the incident concerns research at NCHS or NIOSH, then it should be reported to the NCHS ERB or NIOSH HSRB administrator. (Further references to HRPO in this section similarly include corresponding NCHS and NIOSH staff.) This message should include the following:
 - the CDC protocol number
 - a statement that an incident is thought to have occurred
 - the site of occurrence
 - a brief description of the nature of the incident

The 2 working days between CDC’s awareness and notification to HRPO may include internal review and other CIO-specific procedures. The program may determine that certain remedial actions are necessary even before the incident is reviewed by the IRB.

4. On receipt, HRPO immediately notes the incident and prepares for follow-up. Incident reports take highest priority of all administrative actions within HRPO.
5. The CDC IRB administrator immediately notifies the IRB chair and vice-chairs by forwarding the initial e-mail message.
6. In extreme circumstances, the IRB chair and vice-chairs may decide to suspend the study, even before receiving more complete documentation.
7. Within 2 weeks, CDC program staff submit form 0.1254 and any additional documentation to HRPO. Forms must be submitted even if information is not yet complete. Internal CIO-specific procedures should occur within these 2 weeks.
8. HRPO staff note which open incidents await overdue forms and follow up with respective program staff as needed.

9. On receipt of required form(s), the IRB chair and vice-chairs initially determine whether or not the study should be suspended, whether the incident report should be referred to the convened board, and the likelihood that regulatory agencies must be notified.
10. HRPO staff begin drafting notification of regulatory agencies, as needed.
11. The IRB (whether the chair, vice-chairs, or convened board) reviews the incident in detail and takes one or more of the following actions:
 - requests further information
 - requests changes to protocol (requiring form 0.1252)
 - requests notification of other parties, such other IRBs or other study sites
 - suspends the study
 - terminates the study (requiring form 0.1253)
 - recommends whether or not to report the incident to OHRP or FDA
 - accepts the report and actions of investigators
12. Within 1 week of IRB review, HRPO staff complete memorandum to regulatory agencies, as needed, even if action is incomplete.
13. The manager of HRPO or designee signs the memorandum and the memorandum is sent.
14. Follow-up information, action, and reporting may be required, including responses by CDC program staff to the IRB report.

If CDC is relying on a non-CDC IRB, HRPO will coordinate communication with the IRB of record.

4 Responsibilities by role

The responsibilities in the procedures described above may be broken down by role.

CDC investigators:

- Document event in appropriate detail.
- Report promptly to IRB, others as needed.
- Respond to IRB requests.
- Report periodically to IRB, other as needed (including, e.g., safety monitor reports).

IRB:

- Determine whether to suspend the study.
- Request changes to redress problem.
- Accept report.
- Recommend reporting to regulatory agencies.

HRPO (or NCHS or NIOSH, as relevant) staff:

- Prioritize incident reports.
- Facilitate efficient, prompt communication between investigators and IRB.
- Prepare correspondence to regulatory agencies.

Other entities (e.g., safety monitors, data monitoring committee):

- Discharge duties as described in protocol and additional procedures specified in writing outside protocol.

Sponsors:

- Oversee regulatory requirements for human research protections and for marketing approval, as needed.

5 Summary review of procedures

1. Incident happens.
2. CDC becomes aware of incident through active or passive means.
3. Within 2 days, program tells HRPO (or NCHS or NIOSH staff, as relevant) informally by e-mail.
4. Within 2 weeks, program sends O.1254, possibly with supplemental information.
5. IRB takes action.
6. HRPO reports to regulatory agencies, as needed.
7. Follow-up occurs until incident is sufficiently remediated.

Form 0.1254: Incident report

- 1 Protocol identifiers
- 2 Key CDC personnel
- 3 Characterization of incident
 - 3.1 Reporting category
 - 3.2 Timing of occurrence and awareness of incident
 - 3.3 Site of incident occurrence
 - 3.4 Description of incident
 - 3.5 Actions taken to address incident
 - 3.6 Other entities to whom this incident is being reported by investigators
- 4 Additional comments

Form 0.1254 is required for all reportable incidents. Additional information on adverse events may be submitted in any format, including form 0.1254S. Form 0.1254S is meant to capture many elements prescribed by ICH guidelines E2A. This format may be useful for supplementing an incident report as well as for other reporting purposes, such as to a sponsor or regulatory agency reviewing for marketing approval.

1 Protocol identifiers

Complete the protocol ID and title fields with information found in the CDC HRPO protocol tracking database.

2 Key CDC personnel

This section is for describing CDC personnel associated with this study or this report. For HRPO's purposes, CDC personnel include CDC employees, fellows, and on-site contractors.

The *primary contact* is the person who will receive protocol-related communications from HRPO. Provide the name (optionally including degrees), CDC user ID, Scientific Ethics Verification number (SEV #), and CDC unit including the national center (or equivalent, including NIOSH, NIP, the Office of Genomics and Disease Prevention, and ATSDR) and division (or equivalent). This row must not be left blank.

The *principal investigator* (PI) is the person who accepts responsibility for the ethical conduct of this project, and for complying with the governing regulations (45 CFR part 46 or 21 CFR parts 50 and 56). Fill in the name (optionally including degrees), CDC user ID, CDC SEV #, and CDC unit. If there is no PI at CDC, enter "none". If the PI is the same as the primary contact, enter "same". If the PI and primary contact are different people, both will receive correspondence from HRPO.

The person completing the report is indicated in the third row. If the same person's name should appear in 2 consecutive rows, the second row may be marked "same". Fill in the name (optionally including degrees), CDC user ID, CDC SEV #, and CDC unit.

3 Characterization of incident

This section contains several subsections for providing information that may be relevant to the incident that is being reported.

3.1 Reporting category

This section indicates the reason or reasons the incident is being reported to the IRB. All relevant reasons should be indicated. In addition, if one or more incidents have previously been reported to

the IRB for this protocol, mark one or both recurrence check boxes according to whether previous incidents had or did not have any similarity or relationship to the current incident being reported.

3.2 Timing of occurrence and awareness of incident

This section contains 3 rows intended to capture 3 time periods: when the incident occurred, when the site became aware of the incident, and when CDC staff became aware of the incident. In each case, if there is a single date, report it in the left column. If there is a date range, report the beginning of the date range on the left, and the end of the date range on the right. An optional text field is provided for further explanation if needed. This may be useful for incidents whose timing cannot be adequately captured by a date range.

3.3 Site of incident occurrence

This section captures information about the institution at which the incident occurred. The first subsection contains information similar to other CDC protocol tracking forms: support mechanism, institution name, location, and Assurance number. The support mechanism field is a drop-down list, with possible values no support, grant, cooperative agreement, contract/subcontract, purchase order, other funding, identifiable private information, or tangible goods. The OHRP Assurance number is issued by OHRP; if there is no such number, write “none”.

The second subsection captures site-specific information that will be useful in reporting to regulatory agencies: principal investigator, site title, and site tracking number. If the site title is the same, complete the title or write “same as CDC title”.

If the incident occurred at the CDC, then list CDC as the institution name and leave all remaining fields blank.

3.4 Description of incident

This section contains a narrative of the incident itself. As directed on the form, include coded study identifiers of affected participants as appropriate. Describe the current status of the incident, changes in status between initial occurrence and this report, and resolution of the incident, as appropriate. If this incident is an adverse event, also describe in words the seriousness, expectedness, and relationship with study intervention. Finally, mark the check box at the end of this section if this incident changes the harm-benefit profile of the research. In other words, following this incident, does the research appear riskier than had been justified by the potential benefits?

3.5 Actions taken to address incident

This section contains a narrative of how the incident has been or will be remediated. As directed on the form, explain all actions taken, including revisions of the protocol or the consent process. If the protocol or consent process needs to be revised, check the appropriate box(es) and submit a form 0.1252.

3.6 Other entities to whom this incident is being reported by investigators

Briefly describe other entities, if any, to whom this incident is being reported, such as data monitoring committees. If this incident is not being reported to other entities, write “none”. Do not include entities to whom HRPO is reporting the incident, such as OHRP and FDA, unless the CDC program or other collaborators are independently reporting to those entities as well.

This field is meant to give the IRB a sense of how much scrutiny this incident is receiving, and the level of expertise of others reviewing it. If the additional scrutiny is intensive or highly expert, the IRB might defer some judgment to other reporting entities.

4 ***Additional comments***

This is a standard section on each form. Enter any additional comments that will add in the review or tracking of this incident.

Form 0.1254S: Adverse event report supplement to incident report

- 1 Protocol identifiers
- 2 Key CDC personnel
- 3 Characterization of adverse event
 - 3.1 Timing of occurrence and awareness of adverse event
 - 3.2 Site of AE occurrence
 - 3.3 Details of person reporting adverse event
 - 3.4 Sponsor/Company Details (funder or provider of interventional product)
 - 3.5 Participant details
 - 3.6 Suspected intervention (e.g., medicinal products)
 - 3.7 Other interventions
 - 3.8 Description of adverse event
 - 3.9 Analysis of adverse event
- 4 Additional comments

Form 0.1254 is required for all reportable incidents. Additional information on adverse events may be submitted in any format, including form 0.1254S. Form 0.1254S is meant to capture many elements prescribed by ICH guidelines E2A. This format may be useful for supplementing an incident report as well as for other reporting purposes, such as to a sponsor or regulatory agency reviewing for marketing approval.

1 Protocol identifiers

Complete the protocol ID and title fields with information found in the CDC HRPO protocol tracking database.

2 Key CDC personnel

If this form is being submitted in tandem with a completed 0.1254, this section may be left blank.

The *primary contact* is the person who will receive protocol-related communications from HRPO. Provide the name (optionally including degrees), CDC user ID, Scientific Ethics Verification number (SEV #), and CDC unit including the national center (or equivalent, including NIOSH, NIP, the Office of Genomics and Disease Prevention, and ATSDR) and division (or equivalent). This row must not be left blank.

The *principal investigator* (PI) is the person who accepts responsibility for the ethical conduct of this project, and for complying with the governing regulations (45 CFR part 46 or 21 CFR parts 50 and 56). Fill in the name (optionally including degrees), CDC user ID, CDC SEV #, and CDC unit. If there is no PI at CDC, leave the fields in this row blank. If the PI is the same as the primary contact, enter “same”. If the PI and primary contact are different people, both will receive correspondence from HRPO.

3 Characterization of adverse event

3.1 Timing of occurrence and awareness of adverse event

If this form is being submitted in tandem with a completed 0.1254, this section may be left blank.

This section contains 3 rows intended to capture 3 time periods: when the adverse event occurred, when the site became aware of the adverse event, and when CDC staff became aware of the adverse event. In each case, if there is a single date, report it in the left column. If there is a date

range, report the beginning of the date range on the left, and the end of the date range on the right. An optional text field is provided for further explanation if needed. This may be useful for adverse events whose timing cannot be adequately captured by a date range.

If this report provides additional information on an event that was previously reported, indicate by marking the appropriate check box.

3.2 Site of AE occurrence

If this form is being submitted in tandem with a completed 0.1254, this section may be left blank.

This section captures information about the institution at which the incident occurred. The first subsection contains information similar to other CDC protocol tracking forms: support mechanism, institution name, location, and Assurance number. The support mechanism field is a drop-down list, with possible values no support, grant, cooperative agreement, contract/subcontract, purchase order, other funding, identifiable private information, or tangible goods. The OHRP Assurance number is issued by OHRP; if there is no such number, write “none”.

Next complete the site principal investigator.

3.3 Details of person reporting adverse event

Even if this form is being submitted in tandem with a completed 0.1254, this section should not be left blank. This section captures information consistent with ICH guidelines. As directed, provide the name, qualifications, and contact information of person reporting adverse event.

3.4 Sponsor/Company details (funder or provider of interventional product)

This section captures information about the sponsor or the provider of the interventional product. If this applies to 2 separate entities, report on the holder of the IND, IDE, or similar pre-approval number, unless otherwise indicated in the protocol and study procedures.

The identifying regulatory code is the IND or IDE, where FDA is the regulating agency. The sponsor/manufacture code is the internal number used by that entity.

3.5 Participant details

This section captures medical background and other context for the adverse event. As indicated, this information may include the study identifier (but not direct identifiers), sex/gender, ethnicity, race, age, detainment (if applicable, such as in research involving prisoners), anthropometrics (such as height, weight, and other measures), medical condition, and potentially relevant medical history.

3.6 Suspected intervention(s) and

3.7 Other intervention(s)

These sections capture, respectively, the research intervention(s) suspected to be related to the adverse event and other intervention(s) occurring simultaneously with the suspected intervention. For each intervention, give the name(s), indication(s), dosage and route of administration, and information on the start, stop, and duration of exposure.

3.8 Description of adverse event

This section captures clinical details on the event itself, including signs, symptoms, diagnosis; the start, stop, and duration of the event; information on dechallenge and rechallenge; and any

outcome-related information that is available, including recovery, sequelae, and death (with cause of death, if known).

3.9 Analysis of adverse event

This section characterizes the event by severity/seriousness, expectedness, and relation to research procedures. Each subsection contains an optional text field for additional explanation of that characteristic.

4 Additional comments

This is a standard section on each form. Enter any additional comments that will add in the review or tracking of this adverse event.