

**The *Eunice Kennedy Shriver* National Institute of
Child Health and Human Development (NICHD)**

Clinical Research Policy

Guidance Document

Clinical Research Monitoring

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Change History

Date	Version	Change(s)
January 11, 2008	1.1	Added compensation discussion to data monitoring committee section
October 3, 2008	1.2	Clarified nomenclature throughout document; added section on site audits; added template for data monitoring committee charter

1.0 Introduction and Background

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) follows clinical research monitoring guidelines as set forth by four sources: 1) the National Institutes of Health (NIH) policy; 2) regulation through the Code of Federal Regulations (CFR) Title 45 Part 46 that applies to federally funded research; 3) Good Clinical Practice as described in Document E6 of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); and 4) if applicable, relevant U.S. Food and Drug Administration (FDA) regulations. In addition, given the scope of NICHD's research and the various populations studied and served, the NICHD has further refined clinical research monitoring guidelines to provide a more uniform structure for all of its awardees in support of research efforts. The details of NICHD guidelines along with additional supporting information are contained in this document.

The NIH defines clinical research¹ as:

- Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:
 - a. Mechanisms of human disease
 - b. Therapeutic interventions
 - c. Clinical trials
 - d. Development of new technologies
- Epidemiologic and behavioral studies
- Outcomes research and health services research

The NIH defines a clinical trial² as:

A biomedical or behavioral research study of human subjects designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective.

Clinical research monitoring addresses two fundamental principles:

- Ensuring and enhancing the safety of the study; that is, to protect the study participant from unacceptable risk; and
- Assuring the scientific validity of the study; that is, to protect the data and preserve its integrity.

¹ http://grants.nih.gov/grants/funding/phs398/instructions2/p2_human_subjects_definitions.htm

² <http://grants.nih.gov/grants/policy/hs/glossary.htm>

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Monitoring of clinical research studies can be conducted through several approaches. Clinical research which does not evaluate an intervention is usually monitored by the study team using criteria and methods outlined in the study protocol or study plan, the consent form, and the policy and practice of the relevant Institutional Review Boards (IRBs). Clinical research to evaluate an intervention (usually referred to as clinical trials) also are monitored by the study team using criteria and methods outlined in the study protocol or study plan, the consent form, and by the relevant IRBs, **and** may also be monitored by independent entities external to the study team such as a chartered Independent Data Monitoring Committee (IDMC)³ or Data and Safety Monitoring Boards (DSMBs) or by a smaller committee or single medical monitor. (See Section 10.0 for further discussion on IDMCs.)

The NIH has put forth specific guidance for its Institutes to follow regarding data and safety monitoring for clinical trials. Each Institute has a minimum set of responsibilities⁴:

- Prepare or ensure the establishment of a plan for data and safety monitoring for all interventional trials.
- Conduct or delegate ongoing monitoring of interventional trials.
- Ensure that monitoring is timely and effective and that those responsible for monitoring have the appropriate expertise to accomplish its mission.
- Oversee monitoring activities.
- Respond to recommendations that emanate from monitoring activities.

Furthermore, the NIH provides additional guidance on an Institute's performance for data and safety monitoring of clinical trials⁵:

- The Institutes and Centers (ICs) will ensure the integrity of systems for monitoring trial data and participant safety, although they may delegate the actual performance to the grantee or contractor.
- Monitoring must be performed on a regular basis, and conclusions of the monitoring reported to the IC.
- Recommendations that emanate from monitoring activities should be reviewed by the responsible official in the IC and addressed.
- The ICs also have the responsibility of informing trial investigators concerning the data and safety monitoring policy and procedures.
- ICs should require policies that evaluate whether the participants have conflicts of interests with or financial stakes in the research outcome; and when these conflicts exist, policies must exist to manage these in a reasonable manner.

³ Throughout this document, the term Independent Data Monitoring Committees (IDMCs) will be used. This term is sometimes used synonymously with Data Safety Monitoring Boards (DSMBs) or Data Safety Monitoring Committees (DSMCs).

⁴ <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

⁵ <http://grants.nih.gov/grants/guide/notice-files/not98-084.html>

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In reviewing the NIH guidance and noting that some NIH Institutes were developing additional guidance, the NICHD recognized the need to establish Institute-wide policies. The NICHD convened a volunteer group of NICHD staff, who represented a range of disciplines, training, and interests, to review existing NIH policy, other Institutes' materials, and other federal guidelines to make recommendations for the appropriate responsibilities for NICHD awardees for clinical monitoring.

Date Effective

The guidance set forth in this document is effective January 1, 2009, for any new studies initiated under current awards, for all studies initiated under awards starting in the June cycle of fiscal year 2009 and voluntarily applies to current ongoing studies.

2.0 Monitoring Definitions

In an effort to ensure standardization and consistency in clinical research monitoring for studies that evaluate interventions, NICHD has provided the following definitions.

- **Monitoring:** Assuming responsibility for reviewing events and outcomes during the implementation of a study in two domains: 1) safety of participants; and 2) integrity and quality of data including study accrual. Study monitoring encompasses comparing events and outcomes to pre-defined criteria. If the study events and outcomes indicate deviance from those criteria, study monitoring would mandate making a recommendation to alter the study implementation.
- **Routine Monitoring:** The study team has responsibility for monitoring the study typically based on a monitoring plan incorporated in the study protocol or study plan, IRB oversight, institutional oversight in compliance with applicable institutional, state and federal guidelines, policies, regulations and laws. (See Section 5.0 for criteria to apply Routine Monitoring).
- **Supplemental Monitoring:** In addition to routine monitoring, and depending on the nature of the research, monitoring can be effectively augmented through mechanisms and independent external entities such as a single-person Medical Monitor, a small Study Monitoring Committee, a multidisciplinary committee or a chartered multidisciplinary team such as an IDMC. (See Section 6.0 for criteria to apply Supplemental Monitoring.)

3.0 Roles

The NICHD recognizes that many key stakeholders are involved in clinical research and are engaged in many roles. As a general practice, no individual should have multiple roles in a clinical research study. For example, the same person should not be the primary caregiver for study participants as well as function as the principal study monitor. In addition, the role of monitor must be one free from any potential or actual conflicts of interest so that independence and objectivity are maintained. For further discussion of roles, independence, and conflict of interest, refer to the NICHD guidance document on Conflict of Interest in Clinical Research.

The NICHD recognizes the integral role of the NICHD Program Officer (PO) in the monitoring process for clinical research. The PO shall not have the role of a formal study monitor for any particular study in her or his portfolio; however, the PO should be formally engaged in the monitoring process, regardless of whether the monitoring is routine or supplemental. The PO

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should act as a point of contact for the monitoring body and should receive all required and requested information as outlined in the protocol and under applicable charters, policies, regulations, and laws.

4.0 General Principles for Clinical Research Monitoring

The NICHD policy is based on two general research principles:

- Ensuring and enhancing the safety of the study; that is, to protect the study participant from unacceptable risk; and
- Assuring the scientific validity of the study; that is, to protect the data and preserve its integrity.

To uphold and implement these principles, a monitoring plan must:

- Be proactive and anticipate a range of outcomes and responses; and
- Include a communication plan to support dynamic interaction between relevant parties, including monitors, investigators, sponsors, the NICHD, regulatory authorities, and others.

5.0 Routine Monitoring Requirements

Study Protocol Requirements

All clinical research studies are expected to conduct monitoring based on a study-monitoring plan (additional supplemental monitoring requirements for some clinical trials are in Section 6.0). Each study must develop a monitoring plan that is included in the study plan or protocol that defines:

- How the study will comply with regulatory requirements
- The specific events and activities that will be monitored
- The roles and responsibilities for everyone on the team who is involved in monitoring
- Who has responsibility for reporting (and who they report to)
- A schedule for monitoring
- If applicable, the type and number of events that would halt accrual and would generate a review of eligibility, monitoring, assessments, intervention, and how the resumption of accrual would occur

If the monitoring plan information is found in institutional or consortium or network standard operating procedures and documents, then the study protocol does not need to repeat the information; however, at a minimum, the study protocol should have a brief summary of the monitoring plan with a reference to the applicable standard operating procedures.

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The NICHD expects that each study plan or protocol will include a list of expected adverse events regardless of whether these adverse events are referenced or explained in other types of study documentation. A list or description of *expected events* should be in the following forms:

- A description of the scope of expected adverse events of the underlying condition based on either a recent literature review or textbook. If none are expected during the study time frame, simply state that no adverse events are expected;
- If interventional products are administered, a description of the safety profile for *each* product administered in the study (investigational and marketed) including, if known, the frequency, severity, and duration of adverse events;
- If assessments (for example, a blood test, imaging study, survey instrument, etc.) that are not part of the routine care of the disease or underlying condition are scheduled in the study, then the known risks and complications from those assessments should be listed in the study protocol. The best quality information to include in the study protocol regarding that assessment would be individual institutional experience using the assessment at the study site, which includes the total number of people that received the assessment plus the complication rates. If institutional experience is not available, published data from similar studies and published data on the general use of the assessment tool or technique may be substituted; and
- An integrated listing of adverse events containing those anticipated from the natural history plus those anticipated from any and all interventions and assessments that may occur on study.
 - The potential advantages of an integrated list of expected events are:
 - ▶ IRBs could readily assess the overall risks from a study.
 - ▶ Informed consent process and documents could be prepared to better inform prospective study participants of potential risks.
 - ▶ Adverse event reporting could be simplified by comparison of an event with a single source document.

6.0 Criteria to Initiate Supplemental Monitoring

The NICHD expects clinical research with any of the following criteria to establish a supplemental monitoring entity:

- Late phase clinical trials statistically powered to establish efficacy. Late phase clinical trials are generally large studies, but not necessarily so, and are designed to affect current medical practice, product labeling if applicable or public health policy. Late phase studies are expected to have supplemental monitoring through an IDMC.
- Multi-site/multi-center clinical trials. Multi-site/multi-center clinical trials involve separate institutions using the same study protocol. Several sites that are within the same legally established institution are not generally considered to be a multi-site study. Multi-site clinical trials are expected to have supplemental monitoring through an IDMC. Exceptions to oversight using an independent data monitoring committee will be considered for multi-site clinical trials if it can be established that the intervention poses

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minimal risk to research participants, as defined in 45 CFR Subpart A, Sec. 46.102, and there is minimal risk to data integrity and quality (for example—small number of sites, small sample size, few data elements, short duration). In such cases, supplemental monitoring can be accomplished through alternative mechanisms such as the use of an *ad hoc* or standing Study Monitoring Committee or Medical Monitor. Requests for exceptions should be made in writing to the relevant NICHD Branch and a determination will be made and documented by the NICHD Branch chief in consultation with the applicable NICHD Center director(s).

- Clinical trials involving randomized treatments. Multi-arm clinical trials that use randomization are designed to minimize potential bias in the interpretation of the results. Randomization implies scrupulous attention to the details of study implementation to avoid any compromise in data integrity. Randomized studies are expected to have supplemental monitoring through an IDMC. Exceptions can be made if the study involves only minimal risk to participants, as defined by 45 CFR Subpart A, Sec. 46.102 and minimal risk to data integrity and quality (for example—small number of sites, small sample size, few data elements, short duration). In such cases, supplemental monitoring can be accomplished through alternative mechanisms such as the use of an *ad hoc* or standing Study Monitoring Committee or Medical Monitor. Requests for exceptions should be made in writing to the relevant NICHD Branch and a determination will be made and documented by the NICHD Branch chief in consultation with the applicable NICHD Center director(s).
- Clinical trials involving vulnerable populations, such as those who are children, pregnant women, elderly and ill, terminally ill, or of diminished mental capacity, or any population otherwise unable or unlikely to provide informed consent that are at greater than minimal risk. If the clinical trial involves only minimal risk to participants, as defined by 45 CFR Subpart A, Sec. 46.102 and minimal risk to data integrity and quality (for example—small number of sites, small sample size, few data elements, short duration), monitoring can be accomplished through alternative mechanisms, such as the use of a detailed monitoring plan in the protocol. Requests for exceptions should be made in writing to the relevant NICHD Branch and a determination will be made and documented by the NICHD Branch chief in consultation with the applicable NICHD Center director(s).
- Clinical trials in which the treatment is particularly invasive or has other serious safety concerns (e.g., may result in serious toxicity) are expected to have an IDMC.
- Clinical research studies in which an assessment that is used solely for research purposes is considered greater than minimal risk are expected to have an IDMC.
- Clinical research studies, including observational studies in which participants are already at elevated risk of: (1) death; (2) life-threatening conditions (that is immediate risk of death); (3) in-patient hospitalization or prolongation of existing hospitalization; (4) persistent or significant disability/incapacity; or (5) congenital anomaly or birth defect. These events are considered Serious Adverse Events by regulatory authorities. Studies with the likelihood of occurrence of Serious Adverse Events are expected to have supplemental monitoring through an IDMC. Exceptions can be made if the study involves only minimal additional risk to participants, as defined by 45 CFR Subpart A, Sec. 46.102 and minimal risk to data integrity and quality (for example—small number of sites, small sample size, few data elements, short duration). In such cases, supplemental

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monitoring can be accomplished through alternative mechanisms such as the use of an ad hoc or standing Study Monitoring Committee or Medical Monitor. Requests for exceptions should be made in writing to the relevant NICHD Branch and a determination will be made and documented by the NICHD Branch chief in consultation with the applicable NICHD Center director(s).

- A clinical research project that is of sufficiently long duration that protocol changes may need to be considered based on changing medical practice or interim analyses are expected to have an IDMC.
- Any clinical trial in which members of the study team have a stated or perceived conflict of interest is expected to have an IDMC.

7.0 Ongoing Study Monitoring and Site Audits

The general purpose of ongoing study monitoring during the course of a study is to assure accuracy and completeness of information integral to the assessment of study outcome and regulatory compliance. Examples of the types of information that may be audited include:

- Patient eligibility
- Compliance with protocol defined assessments and, if applicable, interventions
- Overall quality of record keeping
- Concomitant therapy or other information which might affect study results but is not recorded on submitted study forms
- Adequacy, if applicable, of investigational drug handling and drug accountability records

The proportion of records to be audited and the frequency of auditing are functions of the risk and complexity of a study. In general, auditing at the beginning of a study is more likely to result in an opportunity to take corrective action. There is not an expectation to perform 100-percent auditing of all data collection, which is resource intensive, by regulatory agencies. Also, conducting audits on 100 percent of enrolled study participants or collected data has not been formally demonstrated to be superior to selective auditing in reducing bias and uncertainty in study outcomes.

Factors to consider in selecting sites, frequency, and extent of auditing are dependent upon the risks and complexity of the study, the experience and track record at individual sites, and the potential resource and time impact on the overall study and overall scientific program. The availability of electronic health records and data transfer options may facilitate the process by permitting remote audits.

The use of a study monitor or IDMC can be a component of ongoing study monitoring by structuring interim data analyses to compare expected to observed events or event targets. Variations from expected events can be used as triggers for further monitoring and auditing.

For a program with multiple studies, an alternative to study by study auditing is to consider study site auditing on a periodic basis to review all studies at a given site to ascertain general site

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quality and compliance. For example, a three year cycle for site evaluation is considered acceptable by the National Cancer Institute.

8.0 Reporting Requirements for Adverse Events

Federally funded clinical research studies are required by Federal regulations to report adverse events to the Office for Human Research Protections (OHRP), and to the FDA, if FDA-regulated products such as a device, drug, or biologic are used. Both agencies are human protection (risk assessment) oriented, and therefore require the reporting of any events in a study that may affect or compromise participant safety. NICHD-funded studies will always be conducted under OHRP regulations, and if applicable, also under FDA regulations.

OHRP Requirements

The OHRP uses the term “unanticipated problem.” The OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets *all* of the following criteria:

- Unexpected;
- Related or possibly related to participation in the research; and
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) *than was previously known or recognized*.

The notion of “unanticipated problems involving risks to subjects or others” is found but not defined in the U.S. Department of Health and Human Services (HHS) regulations at Title 45 of the CFR, part 46.

OHRP considers adverse events to be caused by one or more of the following:

- Procedures involved in the research
- Underlying disease, disorder or condition of the subject; or
- Other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

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

The OHRP considers adverse events that are unexpected, related, or possibly related to participation in research, and *serious* to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a *greater risk* of physical or psychological harm than was previously known or recognized. Such events routinely warrant consideration of substantive changes in the research protocol or informed consent process or other corrective actions in order to protect the safety, welfare, or rights of subjects.

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The OHRP definition of “serious” includes an event that

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Results in a congenital anomaly/birth defect; or
- 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.

The OHRP states that the following situations require reporting in a specified time frame:

- Unanticipated problems that are serious adverse events should be reported to the IRB within **one week** of the investigator becoming aware of the event.
- Any other unanticipated problem should be reported to the IRB within **two weeks** of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee) (for NICHD-supported research, the NICHD PO), and OHRP within **one month** of the IRB’s receipt of the report of the problem from the investigator.

FDA Requirements

The FDA uses the term “adverse event” although it is not explicitly defined in the FDA regulations under Title 21 of the CFR. The FDA defines adverse events in guidance documents in a manner consistent with the definitions in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2A Clinical Safety Data Management (Definitions and Standards for Expedited Reporting published in 1994):

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.

Other definitions that may be relevant when discussing FDA requirements:

- Adverse event for an Investigational Agent: All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ICH E 2A).
- Adverse event for a Marketed Product: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis,

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or therapy of disease or for modification of physiological function (World Health Organization Technical Report 498 [1972]).

The FDA definition of *Serious Adverse Drug Experience* is consistent with the ICH and is defined as any adverse drug experience occurring at any dose that results in:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity; or
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.⁶

Product Under an Investigational New Drug (IND) Application

For a product under an IND application or Notice of Claimed Investigational Exemption for a New Drug, as defined in Title 21 of the CFR, Section 312.3, the definition of an “unexpected adverse drug experience” based on applicable regulations is: any adverse drug experience, the specificity or severity of which is not consistent with the *current investigator brochure*; or, if an investigator brochure is not required or available, the specificity or severity of which is *not consistent with the risk information described in the general investigational plan* or elsewhere in the current application, as amended.⁷

Associated Use

The FDA addresses the concept of events that are associated with the use of a product when studies are performed under an IND application. An event is considered “associated with the use of” the product when there is a reasonable possibility that the experience may have been caused by the product.

As a matter of policy, serious adverse events that occur within 30 days of administration of the last exposure to the product are generally interpreted as “associated with the use of.”

FDA Licensed Product

For an FDA-licensed product, an adverse experience is defined as: any adverse experience that is not listed in the *current labeling* for the product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but that differ from the event because of greater severity, duration, or specificity.⁸

⁶ Source: 21CFR312.32 & 314.80 and ICH E2A

⁷ Source: 21CFR314.80(a)

⁸ Source: 21CFR314.80(a)

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For studies using FDA-licensed products there is no requirement for establishing an association of the event and use of the product; thus, all adverse experiences that are not listed in the approved product package insert are reportable.

FDA Reporting of an Event Based on Published Literature Reports

The FDA Marketed Products literature requires a 15-day Alert report be filed with the FDA based on information from the scientific literature (found in scientific and medical journals either as case reports or as the result of a formal clinical trial) on serious and unexpected adverse drug experiences and is required to be accompanied by a copy of the published article.⁹

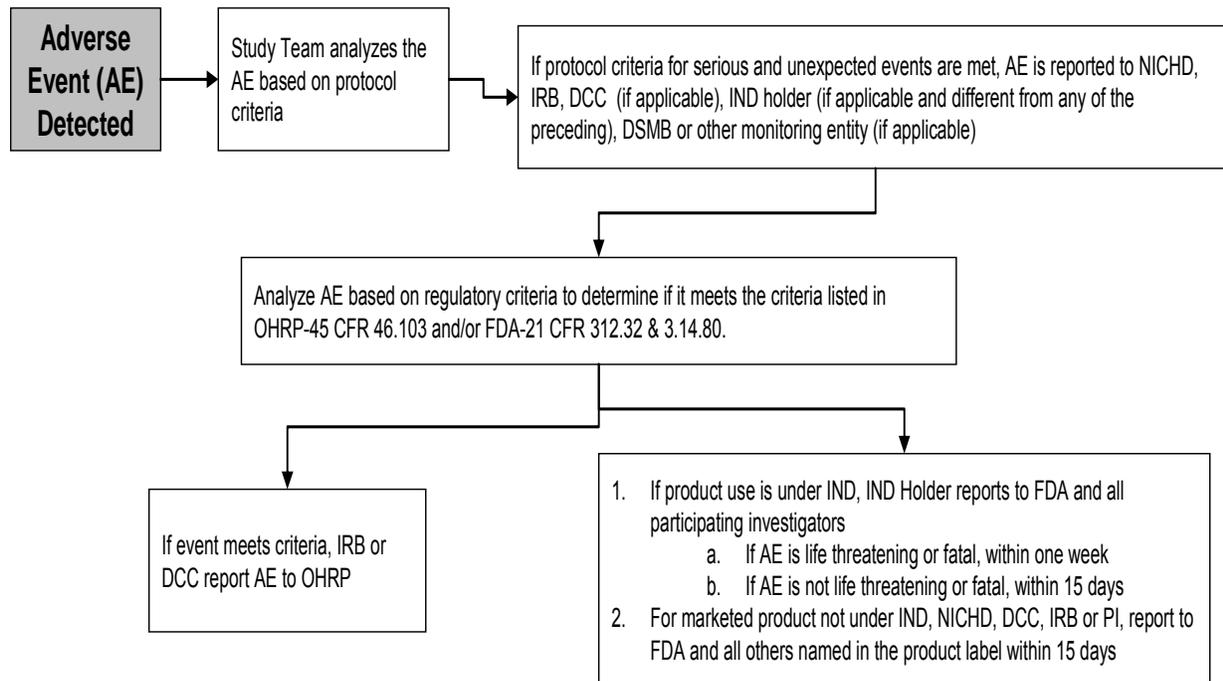
Summary of Definitions & Requirements

The following table summarizes the definitions and expedited reporting requirements for adverse events.

Agency/Type of Problem	OHRP: Unanticipated Problem	FDA IND: Adverse Product Experience	FDA-Marketed Product: Adverse Product Experience
File an Expedited Report if the event is:	Unexpected based on protocol related documents or natural progression of disease or condition	Unexpected based on investigator's brochure or protocol	Unexpected based on approved package insert
AND the event is:	Possibly related to the study	Associated with the use of the product	No requirement for establishing association of the event with product use
AND the event is:	Greater risk of harm than was previously known or recognized	Serious	Serious
Reporting Requirements	To IRB: Within one week: If unanticipated problem is a serious adverse event Within two weeks: if other unanticipated problem To OHRP and others: Within one month	To FDA and all participating investigators: Within one week: if fatal or life threatening Within 15 days: if other event	To FDA and others named in product label: Within 15 days

⁹ Source: 21CFR314.80(d)

Study Steps to Reporting Adverse Events



Legend: AE = Adverse Event; CFR = Code of Federal Regulations; DCC = Data Coordinating Center; DSMB = Data and Safety Monitoring Board or Independent Data Monitoring Committee; FDA = Food and Drug Administration; IND = Investigational New Drug application; IRB = Institutional Review Board; OHRP = Office for Human Research Protection; NICHD = *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; PI = Principal Investigator

9.0 Harmonization of Policy and Practice with Other NIH Institutes and Centers

The NICHD conducts some of its research studies in conjunction with other NIH Institutes or other entities. The NICHD will assume responsibility on a case-by-case basis for harmonization and clarification of expectations regarding study monitoring expectations, if needed.

10.0 Independent Data Monitoring Committees (IDMCs)

The following types of studies are expected to operate under the supervision of a chartered IDMC:

- Late phase clinical trials statistically powered to establish efficacy
- Multi-site clinical trials
- Randomized clinical trials
- Clinical trials greater than minimal risk involving vulnerable populations, such as children, pregnant women, elderly and ill, terminally ill, or those of diminished mental capacity

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- Clinical trials in which the intervention is particularly invasive or is associated with other safety concerns
- Clinical research studies with an assessment used solely for research purposes that is considered greater than minimal risk
- Studies in which participants are already at elevated risk of: (1) death; (2) life-threatening (that is immediate risk of death) conditions; (3) in-patient hospitalization or prolongation of existing hospitalization; (4) persistent or significant disability/incapacity; or (5) congenital anomaly/birth defect
- The study is of sufficiently long duration that protocol changes may need to be considered based on changing medical practice or interim analyses
- any clinical trial in which members of the study team have a stated or perceived conflict of interest

An IDMC operates under a charter outlining the roles, responsibilities, and standard operating procedures for the group. The charter will:

- Define the roles, responsibilities, and relationships for each of the members.
 - The charter will outline the members and designate whether members are voting members or advisory members, who may attend open and closed sessions, the line of authority for reviews and decision making, who is granted access to certain data (e.g., blinded and un-blinded), the compensation for IDMC members, and any potential conflicts of interest.
 - The charter will outline the responsibilities of the group including: familiarizing group members with the study protocol and monitoring of adverse events, data quality, participant recruitment and enrollment, the risks and benefits, reporting, etc.
 - The charter may also include an organizational chart depicting the relationships between all of the major stakeholders of the study team, the study sponsor, the funding organization, and the IDMC.
- Identify the standard procedures for each of the following items:
 - Decision-making procedures, including lines of authority
 - Meeting frequency and format, including logistics and required attendees/quorum
 - Procedures for unscheduled evaluations, including types of events that would trigger an unscheduled evaluation, expected information, involvement of the study chair, required number of members, and communication of recommendations
 - Statistical procedures that may be utilized by the IDMC, including any stopping rules based on benefit or harm, futility analysis, or decision points in adaptive designs
 - Monitoring of recruitment goals
 - Methods for making recommendations to the study sponsor and investigators, funding organization, and other relevant parties

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- Guidelines for reporting on decisions or key outcomes (both scheduled and unscheduled)
- Preparation and dissemination of meeting materials, including pre-reading, meeting minutes, and follow-up reports
- Vehicles for communication between all involved parties
- Maintenance of proper documentation

In addition, the charter may provide templates or forms of the documentation listed below. It should also identify who will maintain the completed documents:

- Confidentiality agreement(s) signed by all IDMC members
- Conflict of Interest (COI) statement signed by all IDMC members
- Format and content of the minutes of all IDMC meetings
- Format and content of all IDMC reports
- Procedure for amending the IDMC charter
- Procedures for record-keeping and archiving¹⁰

For advice on preparing an IDMC charter and procedures, please contact the relevant NICHD PO. In addition, the FDA provides researchers with a guidance document, *Establishment and Operation of Clinical Trial Data Monitoring Committees*.¹¹ The FDA's guidance documents do not constitute legally enforceable responsibilities; however, the NICHD encourages its awardees to review and adhere to this guidance, especially when conducting clinical trials for which the FDA provides regulatory oversight. The guidance documents describe FDA's current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance documents signifies that something is suggested or recommended, but not required.

IDMC Responsibilities

The IDMC should meet prior to the enrollment of the first study participant to familiarize members with the research protocol, ensure the appropriateness of the informed consent documentation, and understand the proposed plan for safety and data monitoring of the study. In addition, the IDMC should reach agreement on the data that are required for review throughout the study. This decision should be communicated to the study sponsor, investigators, and funding organization in order to ensure its availability.

Throughout the study, the IDMC reviews interim data on both a scheduled and unscheduled basis to detect evidence of efficacy, futility, adaptive procedures, or adverse effects to determine if the trial should continue as originally designed, should be changed, or should be stopped. The IDMC should have procedures for each of these occasions outlined in the charter prior to the

¹⁰ http://www.who.int/tdr/cd_publications/pdf/operat_guidelines.pdf. *Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards*. World Health Organization

¹¹ Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Data Monitoring Committees, FDA, March 2006

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enrollment of any study subjects. The IDMC evaluates and reports on the progress of the trial, including periodic assessments of data quality and completeness, monitoring of recruitment goals, adherence to study protocol, accrual and retention of participants, occurrence of adverse events, and other factors that may affect the study outcome.

The IDMC is also responsible for reviewing any major proposed modifications to the study prior to its implementation. The IDMC must maintain the confidentiality of the study participants, trial data, and results of the monitoring.¹²

For any NICHD funded study that the IDMC recommends *stopping accrual or closing the study*, the Director of the Institute or designee will take the recommendation into consideration and will make the final determination. Other IDMC recommendations will be implemented according to procedures outlined in the charter.

Examples of IDMC responsibilities are:

- Review the research protocol, review model informed consent documents, and plans for data and safety monitoring, including all proposed revisions;
- Review methodology used to help maintain the confidentiality of the study data and the results of monitoring by reviewing procedures put in place by investigators to ensure confidentiality;
- Monitor study design, procedures and events that will maximize the safety of the study participants and minimize the risks ;
- Evaluate the progress of the study, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of the study site(s), and other factors that may affect study outcome;
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the studies;
- Review serious adverse event documentation and safety reports and make recommendations regarding protection of the safety of the study participants;
- Report on the safety and progress of the study;
- Evaluate and report on any perceived problems with study conduct, enrollment, sample size, and/or data collection;
- Provide a recommendation regarding continuation, termination or other modifications of the study based on the cumulative experience including the observed beneficial or adverse effects of the treatment under study;

¹² http://web.mit.edu/crc/www/Guidelines_MIT.doc

IDMC Membership

Each member's role will be identified at the time of appointment regarding their role as a voting member or advisory member. The Chair of the IDMC will be selected from among the voting members according to the charter.

Voting members of the IDMC can include physicians, statisticians, other scientists, and lay representatives selected based on their experience, reputation for objectivity, absence of COIs, and knowledge of clinical research methodology. Additional program and statistical staff from the NICHD may be permitted to serve as advisory members to the IDMC as outlined in the charter and as consistent with NICHD policies regarding COI.

Frequency, Records, and Summaries of Meetings

Meetings of an IDMC should be scheduled based on the perceived risks and need for oversight and scheduled interim analyses. A typical frequency is every 12 months, or every 6 months for studies that warrant additional monitoring. *Ad hoc* meetings can be called as needed, and a procedure, quorum, and means of communication for such events should be described in the charter.

Interim analyses, particularly for studies with an adaptive design, may be triggered by a time benchmark or an event benchmark. If the interim analysis is event driven, for example a number of patients that had a particular benefit or a particular adverse event, the procedure for scheduling a meeting of the IDMC and the disposition of the study between the benchmark and the recommendation of the IDMC should be described in the charter.

The disposition of documents submitted to an IDMC to prepare for a meeting is generally classified as for open session or closed session. The specific disposition of documents should be described in the charter, particularly those prepared for closed session.

All meetings should have a summary of record that the meeting occurred, noting date and time and means of communication (e.g., in person, teleconference, videoconference or hybrid), participant list, list of studies discussed, and recommendations. The summary document should be communicated to the relevant parties as described in the charter and should include general outline of contents, order of communication to designated recipients, and time frame for communication. The location and duration for archiving IDMC meeting summaries should be outlined in the charter. A typical IDMC charter includes a description of the archiving procedure for both communicated documents and summaries of closed-session discussions. The separation of the two types of documents helps protect against inadvertent communication outside the IDMC of confidential data, such as study arm assignments.

Communication of IDMC recommendations should generally occur first to the study sponsor, such as the NICHD, or to the study steering committee. It is then the responsibility of the study sponsor or study steering committee to inform others, such as other study investigators, IRBs, and regulatory authorities of the IDMC recommendations. In some cases, particularly when an IDMC is affiliated with an institution and monitors multiple studies, the IDMC may communicate directly with the relevant IRB.

Comments, Questions, or Suggestions

Comments, questions or suggestions regarding the content in this document should be directed to Steven Hirschfeld, M.D., Ph.D., Associate Director of Clinical Research, NICHD, at hirschfs@mail.nih.gov.