SUBJECT: Data and Safety Monitoring **POLICY:** RA:HRPP:08.09

DATE EFFECTIVE: **PAGE:** 1 of 2

I. POLICY

In accordance with Federal regulations (45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6); U.S, Department of Defense Directive 3216.02), it is the policy of the Children's National Medical Center (CNMC) Institutional Review Board (IRB) to require, when appropriate, that research plans make adequate provision for monitoring the data collected to ensure the safety of subjects.

The IRB must determine that the data and safety monitoring plan is adequate to protect research subjects in order to approve the research.

II. ACCOUNTABLE EXECUTIVE AND REVIEWER(S)

A. Accountable Executive: Chief Academic Officer/Institutional Official for the Federalwide Assurance
B. Department Responsible for Review: Office for the Protection of Human Subjects
C. Committee Responsible for Review: Institutional Review Board Executive Committee
Research Policy/Procedure Working Group

III. APPROVAL

Approved by:

IRB Executive Committee — 3/8/2010
Date

Research Policy/Procedure Working Group — _____
Date

_____ — _____
Mark L. Batshaw, M.D., Chief Academic Officer — Date

IV. APPLICABILITY

Areas where the policy and procedure applies: Children's Research Institute, Children's National Medical Center

Persons to whom the policy and procedure applies: Institutional Review Board, investigators

V. REVIEW OR REVISION DATE

Original:

VI. REFERENCES

AAHRPP Element(s):

Federal Regulations: U.S. Department of Health and Human Services (DHHS) 45 CFR 46.111(a)(6)
Food and Drug Administration (FDA) 21 CFR 56.111(a)(6)
U.S. Department of Defense (DoD) Directive 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," March 25, 2002, section 4.4.3.

SUBJECT: Data and Safety Monitoring **PROCEDURE:** RA:HRPP:08.09P

DATE EFFECTIVE: **PAGE**: 1 of 7

I. PROCEDURE

A. General Information

1. An important component of human research protection is the monitoring of research once it begins. The Institutional Review Board (IRB) as well as federal funding agencies have emphasized that investigators are responsible for the design and implementation of plans to monitor subject safety appropriate to the degree of risk to the subjects. The IRB is responsible for determining the plan is adequate prior to approving the study (45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6)). Such plans are usually called Data and Safety Monitoring Plans, or DSMPs.

2. The Children's National Medical Center Institutional Review Board (IRB) acknowledges that a variety of types of monitoring may be appropriate depending on the nature, size, complexity, and potential risks of the trial. Some trials will only require the development of a written plan for safety monitoring that can be carried out by the investigators or a medical monitor. However, other protocols will require an independent committee to carry out the data and safety monitoring plan. Such committees are called Data and Safety Monitoring Boards, or DSMBs.

3. A data and safety monitoring plan is an essential component of any scientifically sound clinical research design. The appropriateness of the plan should therefore also be part of the scientific review.

4. The Children's National Medical Center Human Research Protection Program (HRPP) has developed the following guidelines to assist investigators in the design and management of appropriate safety monitoring plans in clinical trials. The guidelines also assist the IRB in its role and responsibilities in reviewing data and safety monitoring plans.

B. Protocols Requiring a Data and Safety Monitoring Plan

1. Data and safety monitoring plans are required for protocols that are determined to be greater than minimal risk. This includes, but is not limited to, prospective clinical trials involving human subjects designed to answer

specific questions about the effects or impact of a particular biomedical or behavioral intervention, such as drugs, treatments, devices, or behavioral or nutritional strategies. Typically these are clinical trials including physiologic, toxicity and dose finding studies (phase I), efficacy studies (phase II), and efficacy, effectiveness and comparative trials (phase III). Pilot interventions with a higher level of risk may also require monitoring plans.

2. Research supported by the U.S. Department of Defense (DoD)

An independent research monitor is required for DoD-sponsored research involving greater than minimal risk (DoD Directive 3216.02, section 4.4.3.), although the IRB can require a monitor for a portion of the project or for DoD-sponsored studies involving no more than minimal risk, when appropriate. Under the DoD regulations:

a) The independent research monitor shall be appointed by name.
b) The research monitor has the authority to:
    i. Stop a research study in progress.
    ii. Remove individuals from a study.
    iii. Take any steps to protect the safety and well being of participants until the IRB can assess the research monitor's report.

See RA:HRPP:09.14 and 09.14P, *Research Supported by the Department of Defense*.

C. Institutional Review Board (IRB) Review of Data and Safety Monitoring Plans

1. The IRB will review the proposed Data and Safety Monitoring plan to assure the adequacy of the Data Safety Monitoring Plan (DSMP) in relationship to the size, complexity, and level of risk of the proposed research.

2. The IRB will also review the qualifications and experience of the medical monitor or the composition of the DSMB, including the qualifications and experience of the individual members. The IRB may make recommendations regarding expertise, frequency of meetings, review materials, or other modifications as deemed necessary, to the investigator for the enhancement of human participant protections.

3. The IRB may request additional information or clarification from the PI regarding the DSMP, medical monitor, or DSMB, if necessary.

4. IRB approval of a protocol will be contingent upon an appropriate data and safety monitoring plan.

D. Determining an Appropriate Data and Safety Monitoring Plan

A sensible data and safety monitoring plan for a particular protocol must be based on the medical, behavioral, or health-related context of the particular study and, in

particular, on the degree of risk to which participants in the research are exposed. Investigators should keep in mind that:

1. The data and safety monitoring process is a broad continuum from monitoring by the principal investigator to the establishment of a Data and Safety Monitoring Board. Monitoring plans should be commensurate with size and complexity of the trial. It is an investigator's responsibility to decide the monitoring plan that is most appropriate for a particular clinical trial taking into consideration the potential risks of the trial.

2. Monitoring may be conducted in various ways or by various individuals and groups, depending on the size and scope of the research effort**.** A Data and Safety Monitoring Plan should include specific policies for determining safe and effective conduct of the trial and specific rules for considering conclusion of the trial when significant benefits or risks have developed or the trial is unlikely to be completed successfully.

3. The following are some examples of data and safety monitoring plans to consider. Please keep in mind these examples are not the only possibilities for a data and safety monitoring plan. The final determination of establishing an appropriate plan will depend on the degree of risk to which participants in the research are exposed and the size and scope of the research effort.
    a) A formal and independent Data and Safety Monitoring Board (DSMB) could consist of a specialist, a biostatistician, and a third uninvolved individual. "Independent" here implies that no individual on the DSMB is associated with the research or any entity that has direct interests in the outcome of clinical research.
    b) Committees and/or individuals could be assigned the explicit responsibility to review adverse events and to perform interim analysis.
    c) For drug/device company sponsored research, Data and Safety Monitoring Boards could be established that include, as a minimum, one individual who has no affiliation with the company sponsoring the clinical trail of a new drug/device/biologic. The Institutional Review Board has the authority to request from the sponsor details of the composition of the data safety board and any potential conflicts.
    d) Individuals unaffiliated with the protocol could be asked to review adverse events. These could be other members of the department/division or colleagues from outside the institution.
    e) Parameters and criteria could be set so that an independent Data and Safety Monitoring Board could be established if a predetermined number of adverse events occur.
    f) A small group of investigators could develop a careful and explicit screening process to review adverse events as they occur.

E. Information for Investigators to Include in a Data and Safety Monitoring Plan

There are four basic features of all Data and Safety and Monitoring Plans:

1. A process to monitor the progress of research and the safety of participants.
    a) A description of the monitoring process should include a number of elements. The plan should include information on the following:
        i. Who actually monitors the trial? If an independent medical monitor is used, identify this individual.
        ii. How often are the data examined in the course of the trial?
        iii. What specific outcomes do the monitors look for?
        iv. What procedures are in place to insure adequate feedback of information to researchers and medical decision-makers, so that research involving excessive risk in relation to anticipated benefits is terminated appropriately?
        v. Is the oversight or supervisory role of investigator/sponsor appropriate?
        vi. What procedures does the institution have for coordinating multi-center trials, if applicable?
    b) With respect to the question who actually has responsibility for monitoring a research protocol, the DSM plan should explain what measures the investigator and sponsor haven taken to prevent potential and real conflicts of interest. This concern is critical when the Principal Investigator (PI), research staff, or sponsor are the only persons monitoring the research, especially when the protocol presents risk.

2. A process for assuring compliance with requirements regarding the detection and reporting of adverse events (AEs).
    a) The minimum required plan for monitoring of adverse events includes:
        i. Scale for grading of the severity of adverse event. (See RA:HRPP:06.01 and 06.01P, *Mandated Reporting to External Agencies*; RA:HRPP:06.02 and 06.02P, *Unanticipated Problems Involving Risks to Subjects or Others, Including Adverse Events*)
        ii. Scale for estimating the relationship of the adverse event to participation in the trial. (e.g. “Very likely/certain association with participation”, “unlikely association with participation”, “Unclassifiable association”, etc.) (See RA:HRPP:06.01 and 06.01P, RA:HRPP:06.02 and 06.02P for examples.)
        iii. Plan for detection and reporting of *unanticipated* adverse events.
        iv. Plan for annual reporting of adverse events.
        v. An overall plan for safety review.
    b) The plan should describe the processes and oversight that the investigator/sponsor has in place for assuring that AE reporting requirements are actually met. For multi-center trials, the plan should outline procedures by which the investigator/sponsor establishes a

central reporting entity that collects and reports AEs to all necessary destinations, including co-investigators at participating institutions and regulatory agencies.

c) The requirements for proper reporting of AEs on clinical research are complex. Possible destinations for AE reports include the Institutional Review Board, the sponsor (if an IND is involved), the FDA (for AEs from commercially available agents), and, if gene transfer is involved, the NIH Office of Biotechnology Activities (OBA).

3. A process for assuring that any action resulting in a temporary or permanent suspension of a clinical trial is reported as soon as possible to the investigator, sponsor and IRB as deemed appropriate.

4. A process for assuring data accuracy and protocol compliance. Investigators should describe what quality-control procedures are in place for assuring data accuracy and completeness in the clinical trial. If an IND or IDE is in place, quality-control procedures are generally stipulated by the IND sponsor and may be simply referenced or summarized in the DSM plan. For studies not done under an IND, the investigator should describe whatever procedures are in place to assure data integrity and protocol adherence. Appropriate procedures may range, for example, from regular data verification and protocol compliance checks performed by a data manager and a principal investigator, to a formal external data-audit process by an agent external to the institution. Examples of outcomes to be included in such compliance procedures might include monitoring whether all enrolled subjects met entry criteria or whether the reasons given for subject drop out of a trial influence the risks, benefits, or validity of the trial as a whole.

F. Responsibilities of a Data and Safety Monitoring Board.

If a data and safety monitoring board is established, it has the responsibility to:

1. Protect the safety of the study participants.

2. Review the research protocol, informed consent documents, and plans for data and safety analysis.

3. Evaluate the progress of the intervention, including periodic assessment of data quality and timeliness, participant recruitment, accrual and retention, and other factors that affect study outcome.

4. Consider factors external to the study when relevant, such as scientific or therapeutic developments that may have an impact on the safety of the subjects or the ethics of the trial.

5. Report on the safety and scientific progress of the trial.

6. Make recommendations to the Principal Investigator (PI) and, if required, to the FDA concerning continuation, termination, or modification of the trial based on the observed beneficial or adverse effects of the research.

7. If appropriate, conduct an interim analysis of efficacy in accordance with stopping rules, which must be clearly defined in advance of the data analysis.

8. Ensure the confidentiality of the trial data and the results of monitoring.

G. Here is some specific guidance on the data and safety monitoring plan for specific types of protocols:

1. **Phase I and II Trials**
   a) In Phase I and II clinical trials, the board will carefully consider the potential risks, complexity, population, and nature of the research in determining whether an adequate DSM plan exists. In phase I and II trials, a number of factors influence risk. For example, a phase I drug trial may involve increasing risk to a small number of participants as the dose is escalated. In phase II trials, there is sometimes information about risks from previous preliminary research, but the risk may be increased as more participants are involved and the disease process may confound the toxicity and outcomes. In phase I and II trials involving potentially high risk or special populations, investigators are obliged to consider additional monitoring standards.
   b) In phase I and II trials, independent DSMBs should be considered when the risks of trial participation are high. In a low risk trial, continuous close monitoring by the investigator may be appropriate provided that there is prompt reporting to the IRB, FDA and sponsor. In some cases, an individual (e.g., medical monitor) may be helpful in the monitoring. In studies involving small numbers of subjects, toxicity may become more apparent through close monitoring of individual patients. In studies involving large number of subjects, potential risks may be better assessed through statistical comparisons of treatment groups.
   c) When phase I and II studies are conducted as multicenter trials, protocols should include a central reporting entity that will be responsible for preparing timely summary reports of adverse events for distribution among site investigators.

2. **Phase III Trials**

   Phase III trials are considered the pivotal research in determining whether a drug or device should go to market. In addition these trials are often multi-center trials with a large number of subjects. For these reasons special precautions need to be taken to assure appropriate monitoring and oversight of the clinical research. *In general the Institutional Review Board will require a*

data and safety monitoring board for phase III trials as a condition of approval.

3. **Gene Transfer Trials**

   The Institutional Review Board will require a DSMB for all gene transfer trials.

II. REVIEW OR REVISION DATE

Original:

III. REFERENCES

AAHRPP Element:

Federal Regulations: U.S. Department of Health and Human Services (DHHS) 45 CFR 46.111(a)(6)
Food and Drug Administration (FDA) 21 CFR 56.111(a)(6)
U.S. Department of Defense (DoD) Directive 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," March 25, 2002, section 4.4.3.

Policies and Procedures: RA:HRPP:06.01 and 06.01P, *Mandated Reporting to External Agencies*
RA:HRPP:06.02 and 06.02P, *Unanticipated Problems Involving Risks to Subjects or Others, Including Adverse Events*
RA:HRPP:09.14 and 09.14P, *Research Supported by the Department of Defense*
RA:HRPP:10.06 and 10.06P, *Investigator Responsibilities for Minimizing Risk, Monitoring Subjects, and Reporting in Greater than Minimal Risk Research*
RA:HRPP:10.11 and 10.11P, *Investigator Responsibilities for Data and Safety Monitoring Plan Requirements*