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I. Introduction

The Division of the Biological Sciences at the University of Chicago has determined that guidelines be established for appropriate oversight and monitoring of the conduct of clinical trials. These guidelines apply to all clinical trials, regardless of study sponsorship or source of support, to ensure the safety of participants and the validity and integrity of study data. The guidelines are based, in part, on the National Institutes of Health (NIH) policy that requires each institute and center to establish a system for appropriate oversight and monitoring of clinical trials that are being supported by Federal funds.

This document is intended to assist investigators in the formulation of a data and safety monitoring plan that can be applied to individual clinical trials. It does not require the use of any particular approach but has been prepared to guide investigators in how to deal appropriately with various clinical trial designs.

Operational definition of a clinical trial:

For purposes of this document, a clinical trial is operationally defined as a prospective study involving human subjects that is designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions. Such studies may include drugs, treatments, devices, or behavioral or nutritional strategies.

In the area of molecular or imaging diagnostics, a study is a clinical trial if it uses the information from the diagnostic test in a manner that somehow affects medical decision-making for the study subject. In this way the information from the diagnostic test may have an impact on some aspect of outcome, and assessment of this outcome may be a key goal of the trial. By contrast, studies that do not use information from the diagnostic test in any manner that can affect the outcome of study subjects, but whose objective is only gathering data on the characteristics of a new diagnostic approach, are not clinical trials and are not covered by this DSM policy, unless performing the diagnostic test itself imposes some risk on study subjects.

Behavioral clinical trials include studies of interventions with the goals to increase behaviors (e.g., cancer screening, physical activity, fruits and vegetable intake), eliminate or reduce behaviors (e.g., smoking, sun exposure) and/or improve coping and quality of life or reduce the negative sequelae of treatment. Observational studies and those that do not test interventions are not considered clinical trials.

Potential benefits of data and safety monitoring include the following:

- **Data Monitoring:**
  - Verify that cohort demographics match pre-study predictions
  - Ensure accrual rates are consistent with pre-study assumptions
  - Ensure event rates are consistent with pre-study assumptions
  - Compare effect sizes with pre-study assumptions
Safety Monitoring:

- Detection of intervention-associated adverse events against disease background
- Identification of unanticipated or unexpectedly severe intervention-associated adverse events
- Recognition of inferior outcome in intervention arm of controlled trial
- Limiting the continuation of futile trials
- Identification of treatment arms or population subgroups at increased risk of adverse outcome

II. Key Elements of a data and safety monitoring plan:

All clinical trials, regardless of study sponsorship or source of support, must have a data safety monitoring plan. The development and implementation of the data and safety monitoring plan is the responsibility of the principal investigator and is subject to review and approval by the Institutional Review Board (IRB). The plan should address the following:

1) Monitoring the progress of trials and safety of the participants:
   Who actually monitors the study and how often is the data examined? What will the monitors review? What procedures are in place to insure adequate feedback of information to researchers and medical decision makers so that trials involving excessive risk in relation to anticipated benefits are terminated appropriately? What oversight or supervisory role of institutional committees exists, if appropriate? Provide a description of how the institution averts or manages any conflict of interest implicit in having a principal investigator (or a direct report of the PI) as the only monitor of a trial that poses significant risk. Information regarding Conflict of Interest can be viewed at [http://www.uchicago.edu/adm/ura](http://www.uchicago.edu/adm/ura)

2) Plans for assuring compliance with requirements regarding the reporting of adverse events.

The FDA defines an adverse event as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The ICH defines an investigational product as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

A Serious Adverse Event or serious drug reaction is any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization
or prolongation of an existing hospitalization or results in persistent or significant disability or incapacity.

The plan should describe the processes and oversight that the PI has in place to assure that AE reporting requirements are met.

For multi-center trials coordinated by a PI at the University of Chicago, the plan should outline procedures by which the PI establishes a central reporting entity that collects and reports AEs to all necessary destinations, including co-investigators at participating institutions. Some of the possible destinations for AE reporting include the IRB, the study sponsor (if an IND is involved), the FDA (for commercially available agents) and, if gene transfer is involved, the NIH Office of Biotechnology Activities (OBA). Note that current federal regulations always require reporting both serious and unexpected adverse events to the IRB.

3) Plans for assuring data accuracy and protocol compliance:

If an IND/IDE is in place, quality-control procedures are generally stipulated by the IND/IDE sponsor and may be simply referenced or summarized in the DSM plan. For studies that are not conducted under an IND/IDE, a description of the procedures that assure data integrity and protocol adherence, for example, how data verification and protocol compliance checks are performed (e.g., by a data manager and the principal investigator, or by a formal internal or external data audit process) should be described.

4) NCI Funded Clinical Trials: The investigator should describe the plan for assuring that any action resulting in a temporary or permanent suspension of the trial is reported to the NCI program director for the grant. (refer to the University of Chicago Cancer Research Center Data and Safety Monitoring Plan). For most investigator-initiated grant applications that support clinical trials in an institution with an NCI-approved data and safety monitoring plan, the investigator should only have to supply the approved institutional plan in the human subjects section of the grant application and describe how it applies to the specific trials.

5) Studies conducted in the General Clinical Research Center (GCRC): Please refer to the Data and Safety Monitoring Guidance Document developed by the GCRC. Refer to the CTO website guidelines page to access the GCRC Data and Safety Monitoring Guidelines and the GCRC Data and Safety Monitoring Plan Application form. For information please contact Anna Klemm, Administrative Assistant at 2-6988 or F. Gary Toback, M.D., PH.D., Research Subject Advocate at 2-1476.

6) Tailoring Institutional DSM Plans to specific studies: The essential elements for a DSM plan outlined above do not stipulate details on how this process should be carried out. It is the responsibility of each PI to develop a DSM plan for each clinical trial that is appropriate to the level of risk to the participants in the trial.

III. Suggestions for monitoring Phase I and Phase II Trials
Investigators should consider reviewing The University of Chicago Cancer Research Center Data and Safety Monitoring guidelines. This document may provide guidance in developing a plan for these studies. A useful tool for monitoring Phase I and Phase II studies could be to establish a periodic conference that can be held at regular intervals for review of individual patient data as well as a summary of descriptive statistics on adverse events and measures of treatment efficacy.

The method and extent of monitoring required should be commensurate with the risks to study participants and should be done regularly. For example, meetings or teleconferences among the participating investigators could be held to review the accumulating data, including accrual rates, serious adverse events (SAE), toxicity and outcome measures. The frequency of the meetings can vary depending on the rate of subject accrual but could occur as often as weekly or bi-weekly for rapidly accruing or high-risk studies. The meetings can either be open or closed. It is suggested that minutes be taken to document decisions made with respect to individual protocols (see Appendix 1 for suggested format). These minutes can be brief and as simple as “The consensus of the group was to continue the protocol without modification”. Attendance at the conference should include the principal investigator or a designee of each study being reviewed. In addition, it may be of value to include a biostatistician, the study research nurse, and if applicable, the director of the clinical trial network under which the trial is being conducted.

The Principal Investigator must provide a general description of the data and safety monitoring plan as part of the protocol submission to the IRB. A section, subsection or appendix of the written protocol must be specifically devoted to describing the monitoring plan. This section, subsection or appendix must be easily identifiable by the IRB reviewers and others responsible for clinical trial oversight. The plan at a minimum must include a description of the reporting mechanism of AEs and SAEs to the IRB, the study sponsor, FDA, and NIH (if appropriate). The data and safety monitoring plan must be reviewed and approved by the IRB before the trial begins. In the event that there is a change in Principal Investigator, the new Principal investigator must submit appropriate documentation that they will accept all aspects of the protocol including the Data and Safety Monitoring Plan.

1. Method for Study Monitoring:

The evaluations should include a review of accrual rates, toxicities and all events requiring AE reports; a description of treatment-related morbidity; and a review of prospectively defined efficacy outcomes. For multi-site studies, summary reports of adverse events should be distributed to the participating sites and the specific institutional IRBs at a frequency dependent upon the nature of the trial and the perceived level of risk.

Phase I dose finding studies present high risk to a small number of participants and therefore require continuous monitoring with frequent reporting. Phase I studies should include a protocol-specified plan for dosage adjustment (e.g., traditional “3+3” rule, modified continual reassessment method, etc.); definition of dose-limiting toxicity; definition of maximum tolerated dose; and plan for reporting of adverse events.

Phase II trials evaluating efficacy involve more participants and, because the disease process can confound interpretation of toxicities, the study may require monitoring by an individual with expertise relevant to the study who might assist in interpreting data to ensure patient safety. This individual must be someone who does not have a vested interest in the outcome of the study, or have any other conflict of interest, financial or otherwise (e.g., such as having a reporting relationship with the PI of the study).
studies should include a monitoring plan for interim analysis of efficacy outcomes to allow for early termination of studies of agents not likely to be active (e.g., Simon’s optimal two-stage design). These plans must be included as part of the protocol and submitted to the IRB before the trial begins. They should also include a description of the reporting mechanisms of adverse events to the IRB, the study sponsor, the FDA, and the NIH as appropriate.

2. Recommendations:

If it is deemed necessary to modify the protocol or terminate a trial due to excess toxicity or lack of efficacy, a letter to this effect should be written by the principal investigator and sent immediately to all participating sites, along with a copy to the respective IRBs.

IV: Data and Safety Monitoring Boards for Phase III Randomized Controlled Trials

For Phase III trials, the establishment of a Data and Safety Monitoring Board (DSMB) is often required to provide an ongoing critical and unbiased evaluation of the progress of the study. A DSMB helps to determine whether the benefits of the investigational intervention have been sufficiently demonstrated, whether the risks are greater than anticipated, or that the level of benefit observed no longer justifies the risks of the research. The DSMB can make unbiased judgments about whether an investigation should be modified to minimize those risks or whether the clinical investigation should be halted. Therefore, an important responsibility of monitoring boards must be for the safety of current and future patients in the trial as well as for all patients who might otherwise use the intervention being tested.

Data and Safety Monitoring Boards (DSMB) will be used primarily for randomized controlled trials but may be appropriate in other settings (e.g., multi-agent Phase II trials across multiple institutions) depending on risks involved, study sponsorship, and potential conflicts of interests. Outside of a randomized controlled trial, interpretation of the need for a DSMB will be primarily left to the discretion of the Principal Investigator, but the IRB or other oversight individuals may recommend that a DSMB be convened.

All clinical trials require safety monitoring (21 CFR 312.32), but not all trials require monitoring by a formal committee external to the trial organizers and investigators. In considering the need for a DSMB, the investigator should address:

a) **The risk to study participants**: A trial that requires a large number of participants is of long duration, and multi-center may require a DSMB because many participants may be at risk over a long period of time.

b) **Assurance of Scientific Validity**: A DSMB can help to assure the scientific validity of the trial. Trials of long duration can be affected by changes over time in understanding the disease, the affected population, and the standard treatment outside the trial. Since the DSMB is the only group reviewing unblinded interim data from a trial, the DSMB is in the best position to recommend to the trial organizers changes in the trial that may be appropriate based on newly available data outside the trial or by accumulating data from within the trial (e.g., event rates).

1. Responsibilities of a DSMB:
a. The primary responsibility of the DSMB is to review interim analyses of outcome data and to recommend whether the study needs to be changed or terminated based on these analyses.
b. The DSMB should consider factors external to the study when relevant information may have an impact on the safety of the participants and the conduct of the study.
c. The DSMB reviews interim toxicity data and adverse events.
d. The DSMB determines whether, when, and to whom outcome data should be released prior to the scheduled reporting of study results at the time specified in the protocol.
e. The DSMB reviews major modifications to the study prior to their implementation (e.g. termination, dropping an arm based on toxicity results, increasing target sample size).

2. Membership:

The ability of a DSMB to assure patient safety and trial integrity depends on its members. The board should be composed of individuals not otherwise connected with the particular clinical investigation. For specific trials conducted under sponsorship of the University of Chicago, the Associate Dean for Clinical Research, after consultation with the Study PI, will appoint DSMB members for a designated term that will extend until all protocol-specified primary events have occurred or as determined by the DSMB based on the study outcomes. The size of the committee should be limited and will be determined by the Associate Dean for Clinical Research.

For NIH cooperative group trials or other multi-center clinical trials sponsored by organizations outside of the University of Chicago, the DSMB is usually appointed by the study leadership in cooperation with the funding agency or by the study sponsor.

The committee will consist of qualified physicians, biostatisticians, appropriate technical or scientific specialists, and health professionals. The Board may include patient advocates as members, and, if deemed appropriate, may invite ad hoc consultants to provide special expertise if necessary. Members should see themselves as primarily representing patient interests. All members will have voting privileges.

3. Meetings:

DSMB meetings will be held at least annually or as required by the timing of the protocol-specified interim analyses. Each randomized trial should have specified interim analysis times and statistical monitoring guidelines incorporated into the protocol. The DSMB will review the status of the trials including accrual, toxicity, efficacy outcomes and the next formal monitoring date as specified in the protocol. The DSMB may elect to meet more frequently if necessary to adequately monitor the trial.

The review of each trial may include three parts. The first part will be an open session in which the principal investigator /and or study team may be present at the request of the DSMB to clarify the status of the study and answer questions. This part will focus on accrual, compliance and toxicity issues. No outcome data may be presented. Following the open session there will be a closed session (second part) limited to DSMB members and the study statistician during which outcome results will be presented by the statistician. Following the closed session, there will be a closed executive session in
which the DSMB discusses outcome results and develops recommendations. All deliberations of the DSMB are strictly confidential.

4. Study Monitoring:

The DSMB has the obligation to ensure optimal therapy for participating patients and optimal conduct of the clinical trial to ensure that subject participation is meaningful. A critical responsibility of the DSMB is accurate and timely knowledge of the progress of the study. The DSMB should be responsible for ensuring that the following procedures are in place:

- Precise tracking of patient accrual
- Ongoing reviews of patient eligibility and evaluability
- Adequate measures to ensure timely submission of study data
- Adequate measures to ensure timely medical review and assessment of individual patient data
- Rapid reporting of serious or unexpected adverse events and treatment-related morbidity information to the IRB and study sponsor
- Interim evaluation of outcome measures and patient safety information

5. Recommendations:

The DSMB should make recommendations based upon the interim results of the study being monitored as well as upon data available to the DSMB from results of other related studies. The DSMB will provide recommendations to the PI to modify the study or continue a study unchanged. If a study modification is proposed, the DSMB should provide the rationale for the recommendation.

a) In the event the DSMB recommends a study modification for patient safety reasons (including early stopping of inferior therapy), the Principal Investigator will implement the change as expeditiously as possible after the Associate Dean for Clinical Research and the Chair of the Institutional Review Board have been informed. In the event the PI does not concur with the recommendations of the DSMB, the Associate Dean will render a judgment regarding the recommendations after consultation with the DSMB, the IRB, the study PI and outside consultants if deemed appropriate. Although the recommendations of the DSMB will not be binding on the investigator, their recommendations along with the comments of the Associate Dean will be transmitted to the IRB whose actions will be binding. In the event the Investigator accepts the recommendation to amend the study, approval of the amendment by the DSMB will be required prior to submission of the amendment to the IRB.

b) In the event the DSMB recommends a study be closed early due to slow accrual, then the recommendation will follow the procedures as described above.

c) In the event the DSMB recommends a change in a study for reasons other than patient safety (e.g., to extend accrual because of an event rate lower than expected) or study closure due to slow accrual, the DSMB must provide an adequate rationale.
Any proposed amendment resulting from such recommendations must be approved by the DSMB prior to submission to the IRB, and documentation of such approval must be provided to the IRB.

6. Confidentiality:

No communication of the deliberations or recommendations of the committee, either written or oral, should be made to anyone outside of the committee, with the exception of the IRB. All DSMB members should sign confidentiality statements and submit conflict of interest disclosure forms. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB (excepting the Associate Dean for Clinical Research and the IRB).

7. Release of Results:

Any planned release of outcome data [to NIH personnel, not members of the committee, or external audiences (e.g., paper presented at professional society meetings, seminars, papers, etc)] prior to final approval of general dissemination of results must be reviewed and approved by the DSMB http://deainfo.nci.nih.gov/grantspolicies/datasafety.htm. In general, outcome data would not be routinely made available to individuals outside of the DSMB until accrual has ceased, all patients have concluded their randomized treatment, and the protocol specified primary endpoint has been reached. The DSMB should be made aware of any communication of analysis of results that do not meet these requirements.

8. Conflict of Interest:

Recognizing that an institutional monitoring system must utilize its own faculty and research staff members to enable the system to function, there is a potential for a conflict of interest to exist. No one who has an indirect or direct relationship to the study being monitored should serve on the DSMB. Individuals invited to serve on a DSMB are responsible for disclosing any potential, real or perceived, conflicts of interest. The University of Chicago has a Conflict of Interest Policy entitled “Outside Professional and Commercial Interests of Faculty/Conflicts of Interest”. This policy addresses situations where there might be a potential financial or personal conflict between a particular outside interest of a faculty member and the obligation that the faculty member owes to the University such that a faculty member’s profit or advantage may come, or reasonably appear to come, at the expense of the well-being of the University. Individuals who are invited to serve on a DSMB are responsible for disclosing, 1) those significant financial interests that would reasonably appear to be affected by or to affect their research or educational activities, and 2) any significant financial interests in entities whose financial interests would reasonably appear to be affected by or to affect the person’s performance of his or her University duties, including participation in a DSMB. Significant financial interests, as defined in the University of Chicago Conflict of Interest Policy, pertain to the financial relationship of investigators to their own research programs. In considering the potential for conflicts of interest and service on the DSMB, individuals should assess their potential conflicts in a broader capacity. Financial relationships that may not present any prospect for bias in their own research
programs may have the potential for bias in oversight of the clinical studies under review by the DSMB. Given the special role the DSMB plays in the assurance of ethical use of human subjects in clinical research, disclosure of potential and perceived conflicts of interest is vitally important. Click here to view the University of Chicago’s policy on Conflict of Interest http://www.uchicago.edu/adm/ura.

The Associate Dean for Clinical Research will review possible conflicts and determine whether there is sufficient basis to exclude an individual from serving on the DSMB or to limit their participation in the DSMB deliberations. Any potential conflicts that may develop during the conduct of the trial should also be disclosed to the Associate Dean for Clinical Research.

9. Oversight:

In order to satisfy the objective of protecting patients, ensuring study integrity and assuring public confidence in the conduct of clinical trials, it is essential the DSMB function in a manner that demonstrates competence, experience and independence of career or financial interests. The Associate Dean for Clinical Research will have oversight of the activities of the DSMB.

References
1. NIH Guide: NIH for Data and Safety Monitoring; June 14, 1999
2. NIH Guide: further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials; June 5, 2000
3. CTEP: Section 2; Roles and Responsibilities for the Conduct of Quality Assurance Programs; March 10, 1999
4. Veterans Administration Cooperative Studies Program
5. NCI Cooperative Group Data Monitoring Committee Policy; July 9, 1996
6. Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials, Controlled Clinical Trials 10:1-10, 1989

Websites
APPENDIX I (A suggested format for minutes)

Data and Safety Monitoring Meeting

Date: __________________________________________________________

Phase and Title of Protocol/IRB Number: __________________________________________________________

Principal Investigator/Designee: __________________________________________________________

Recommendations:

☐ Continue the trial without modification

☐ Accrual:
  ☐ Recommend study be closed because of slow accrual
  ☐ Continue to monitor study, but consider closure because of slow accrual

☐ Recommend study is amended/changed:
  ☐ For patient safety reasons
    ☐ Rate of adverse events
    ☐ Early stopping of inferior therapy
  ☒ To extend accrual because of an event rate slower than expected

☐ Other: __________________________________________________________

Signature/Principal Investigator or Designee: _______________________________________________________