GUIDELINES FOR ESTABLISHING A DATA SAFETY MONITORING PLAN

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A. INTRODUCTION

1. Background

The Institutional Ethics Committee (IEC) of SCTIMST requires investigators to submit a Data and Safety Monitoring Plan (DSMP) for clinical trials as part of the research application. A Data Safety Monitoring Plan is unique to the trial and should be commensurate with the potential risks and with the size and complexity of the trial. The plan is designed to ensure the safety of research subjects and the validity and integrity of the data and may include appointment of an independent Data Safety Monitoring Board (DSMB). These institutional guidelines apply to all protocols and are subject to change due to regulatory or institutional changes.

B. ELEMENTS OF A DATA SAFETY MONITORING PLAN: CONTENT AND GUIDANCE

1. Determination of Study Risk

Determination of risk should include a consideration of both the interventions being performed and the study population. Risk assessments must also take into account special circumstances that are unique to the study such as disclosures of HIV status, results of genetic tests, or surgical procedures.

This document will assist investigators in determining the level of risk and the type of monitoring that will be required.

a) Minimal Risk: All protocols presenting the potential of risk to subjects, even minimal risk, should address how the investigator will monitor risk and report adverse events. A minimal risk study is defined as one where the probability and magnitude of harm and/or discomfort in the proposed research are not more than ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Minimal risk studies may include non-therapeutic studies such as survey research, questionnaires, blood samples (venipuncture or intravenous catheter insertion), observational studies, oral glucose tolerance tests, intravenous glucose tolerance test, routine MRI scans, special diets, exercise testing, ECG's, and anthropomorphic evaluations.

However, survey research and questionnaires may present more than minimal risk to subjects if they address highly sensitive information. Inclusion of special populations (children, prisoners, pregnant women mentally disabled persons, or economically and/or educationally disadvantaged persons) who may be more sensitive or vulnerable to the risks posed by the research, regardless of the study, may increase the level of risk to moderate or high.

b) Moderate Risk: Moderate risk studies exceed the minimal risk, but constitute less risk to the subject than studies with the potential for serious risks to subjects. Moderate risk studies may include phase I, II or phase III multi-institutional trials, studies using drugs for their indicated use, studies that use invasive hemodynamic monitoring with arterial lines, and studies in which blood and tissue specimens are stored. Studies in which blood is drawn for genetic studies, either real time and/or stored for later use are also deemed to present risk to subjects.

c) High Risk: Protocols presenting the potential for serious risks and adverse events may include clinical trials using investigational agents, gene transfer studies, studies using FDA-approved agents for non approved indications; Phase I clinical trials; studies requiring investigator-initiated IND's (investigational new drug) or IDEs (investigational devices); and some Phase II clinical trials.

Also included in this category are studies involving procedures in which there is a high risk for adverse events such as conscious sedation or interventional radiology. Studies in which some or all subjects are at risk of death or severe morbidity because of existing illness or disease are also considered high risk.

2. **Description of Monitoring Plan –** The Principal Investigator is responsible for oversight of the trial(s). For all studies, the following must to be included:

- Monitor(s): The person or persons who should assume monitoring responsibility will depend on the type and risk of the study and may include the investigator, institutional colleagues, outside colleagues, consultants or a combination of the above. Issues of conflict of interest must be addressed, particularly if the investigator him/herself takes on the role of monitor.

- Description of anticipated adverse events (AEs), based on the available data for the clinical trial (this information will also be included in the consent form). Reporting of expected, unexpected, adverse events, and serious adverse events (SAEs). Any serious adverse event will require re-evaluation of the risk determination and continuation of the study

- Interim analysis plan (e.g. how often and by whom are the data examined in the course of the trial).

- Protocol Stopping Guidelines (this is unique to each trial).

- Plan for report on the Data and Safety Monitoring Plan at Continuing Review: This report should include enrollment and drop out rates, protocol deviations, subject interview and conduct, review of subject symptoms and performance status, review of clinical test results, physical examinations, vital signs, diagnostic tests and evaluations.

- The Plan should include procedures for ensuring that data are collected and analyzed per protocol privacy, and that confidentiality of study subjects is maintained.

Monitoring Plan Based on Study Risk

a) Minimal Risk: does not require an independent DSMB. Monitoring is the responsibility of the investigator.

b) Moderate Risk: will, in most cases, require independent safety monitoring. For some strictly genetic studies, in targeted populations, the investigator may serve as the monitor. For small, moderate risk studies, monitoring might be performed by an independent investigator who is an expert in the agent being studied and the patient population. May require DSMB if study is placebo controlled or an investigational agent is used.

c) High Risk: may require a DSMB. For example, in large, blinded studies involving high risk or special populations a DSMB should be constituted. For some high risk studies, monitoring might be performed by a single, independent investigator who is an expert in the agent being studied and the patient population.

C. DATA AND SAFETY MONITORING BOARD (DSMB)

1. DSMB Responsibilities

- The DSMB should meet prior to the enrollment of the first subject to review the research protocol, informed consent documents and plans for safety and data monitoring of the study. This review is to determine the risks and benefits to research subjects, protection and safety of the subjects and to offer suggestions for improving the study design. In addition, the Board should reach agreement on the data that will be required for review. Determination of the schedule of future meetings, appointment of the chair and voting members, who receives minutes, and the signing of conflict of interest statements occur during pre-enrollment meeting.

- The DSMB reviews interim data to detect evidence of efficacy or adverse effects to determine if the trial should continue as originally designed, should be changed or should be stopped based on the data.

- The DSMB evaluates the progress of the trial, including periodic assessments of data quality/completeness, recruitment goals, protocol adherence, accrual and retention of participants and other factors that may affect the study outcome.

- The DSMB protects confidentiality of the study participants, trial data and results of the monitoring.

2. Membership

- The Board should include one or two investigators. If an efficacy assessment is part of the monitoring plan, a statistical monitoring plan is necessary to ensure the validity of the study and the board should include a biostatisitician. The Board membership should have three or five members in total (always an odd number). Investigators are encouraged to consider appointment of individuals from different Units and from other hospitals. The

Board membership does need to be identified at the time of the application submitted to the IEC or prior to enrolling the first subject on the protocol.

- Investigator should give a list of six DSMB members while submitting proposals to Technical Advisory Committee (TAC). On TAC recommendation, IEC will review and approve the DSMB members.

- Qualifications and Responsibilities of Members: Qualifications for membership include: : 1) expertise in the field, 2) experience in conduct of clinical trials and statistical knowledge, 3) independence from the direct management of the clinical trial and 4) no conflict of interest. A chairperson will be appointed and will be responsible for overseeing the meetings, developing the agenda and summarizing the meeting. The chairperson is the contact person for the DSMB.

3. Timing and Frequency of DSMB Meetings

- DSMB meetings will take place at least annually. The Board may meet periodically (quarterly, semi annually, or annually) if the risk to the subject is high, the population is vulnerable, there is a large volume of data to review, and/or after a pre-determined number of subjects have been accrued in the study. The Chairman may also call ad hoc meetings depending on safety or efficacy concerns or when IEC request to evaluate the study.

4. DSMB Meeting

a) DSMB Agenda

i) The Investigator will provide the Board with the information that was determined at the pre-enrollment meeting.

ii) As per the Data Safety Monitoring Plan, The Board will:

- determine adherence to treatment plan
- review interim analysis, if applicable, and determine specific data to be analyzed
- evaluate end point/stop point rules
- review protocol violations and deviations to assess adequacy of study
- ensure documentation of informed consent
- enrollment
  - followed eligibility criteria
  - enrollment numbers
  - visit compliance
  - screening failure information
- discuss investigator or key personnel changes
- review completeness and quality of data collection forms
- evaluate the aggregate analysis of adverse events/serious adverse events
- review vital signs, clinical tests, etc.
- review confidentiality

b) DSMB Meeting Outcome - The major outcomes following data review include:

- Continuing the trial unchanged

- modify the protocols and/or consent form (It may be unethical to continue giving a placebo after a new treatment has been proven to be effective or to continue a new treatment when there is no chance the trial will be positive.)
- terminate the trial

c) DSMB Minutes

Minutes from the meeting should be maintained. The investigator should not be present during decision-making part of the meeting.

Following the Board meeting, a report should be provided to the investigator, the IEC and if necessary, study participants and the Sponsor. The report should indicate whether the study should continue as originally designed, whether the study should be modified to protect patient safety or whether the study should be terminated.