Tata Memorial Centre

Data and Safety Monitoring Sub Committee

Policy and Procedures Manual

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1. Introduction

1.1. Overview

All new cancer-related clinical trial applications proposing to involve TMH subjects (treatment and non-treatment, regardless of sponsorship) must be reviewed and approved by the Hospital Scientific Review Committee and Hospital Ethics Committee.

These guidelines pertain to the scientific monitoring of clinical trials approved by the Hospital Scientific Review Committee and Hospital Ethics Committee.

This process is conducted under the Data and Safety Monitoring Subcommittee of the HEC.

1.2. Clinical trial:

A clinical trial is defined as a prospective study involving human subjects designed to answer specific questions about the effects or impact of particular biomedical or behavioral interventions; these may include drugs, treatments, devices, or behavioral or nutritional strategies. Participants in these trials may be patients with cancer or people without a diagnosis of cancer, but at risk for developing it.

With regard to diagnostic research (molecular or imaging diagnostics), a study is considered to be 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 may have an impact on some aspect of outcome, and assessment of this impact may be a key goal of the trial. 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 the gathering of data on the characteristics of a new diagnostic approach are not clinical trials and are NOT covered by this policy, unless performing the diagnostic test itself imposes some risk on study subjects.

Behavioral clinical trials test interventions aimed at eliminating or reducing human activities associated with enhanced cancer risk, such as tobacco use, poor nutrition, and sun exposure, or eliminating or reducing morbidity associated with cancer screening, diagnosis and treatment.

1.3. Institutional clinical trial:

1.3.1. An institutional (sometimes referred to as investigator-initiated) clinical trial is defined for the purposes of these guidelines as a clinical research study authored by a member of the TMC faculty or staff, not primarily sponsored nor subject to monitoring by an outside agency (e.g. industry, cooperative group, NIH, other institution). Although an investigator may obtain investigational drugs and/or funding from an outside agency or industry in support of the research, if the clinical trial is not subject to monitoring by that agency it will be categorized as an institutional clinical trial and be internally monitored.

1.3.2. Monitoring is conducted on all phase I and II therapeutic institutional clinical trials, regardless of support, and its level is determined by the degree of intervention and risk involved.

1.4. Sponsored/supported, large-scale, multi-site phase III therapeutic intervention clinical trial:

1.4.1. These non institutional trials which involve significant risk, are outside the scope of this system. Independent Data and Safety Monitoring Boards (DSMBs) for such studies would be established by the principal investigator and supported through the funding agency.

1.4.2. Sponsored/supported phase III clinical trials which involve only low risk (i.e. behavioral and nutritional research) would be reviewed on a case-by-case basis, as their sample size may be too large to be practically monitored by this system.

1.4.3. In some cases, these studies would require an independent DSMB.

1.5. Applicability

It is recognized that clinical trials sponsored by some groups and industry are continually audited for compliance and monitored for progress.

Institutional clinical trials without outside sponsorship are the focus of the monitoring system of this committee.

2. Aims and Objectives

As a national cancer center, the TMC needs to ensure that research data generated by the Center investigators are of high quality, reliable and verifiable. To accomplish this objective, the Data and Safety Monitoring Subcommittee is charged with the mission of developing and enacting quality assurance procedures to monitor the overall progress of institutional clinical trials and for ensuring adherence to clinical trial and procedural requirements.

This includes review of the overall progress of each study to insure the safety of participants, validity of data, that the projected accrual goals are met on a timely basis, that excess accrual is avoided, that eligibility and evaluability rates do not fall below minimum acceptable standards, that risks are not excessive, and that adverse events are appropriately monitored and reported to the appropriate agencies.

Inherent in this process is the goal of enhancing the quality of the research by providing the investigator with constructive criticism.

3. Membership

The membership (Appendix I) of the Data and Safety Monitoring Subcommittee is multidisciplinary and shall consist minimally of three physician members and representatives from the various Departments. Any member of the faculty may be co-opted for cases requiring specific expertise.

3.1. The Director TMC shall appoint the Chair/Secretary of the Data and Safety Monitoring Subcommittee.

3.2. Members of the Data and Safety Monitoring Subcommittee shall be appointed by the Subcommittee Chair in consultation with the Director TMC and Chairperson and Secretary of the HSRC and HEC.

3.3. A monitoring team conducts on-site case reviews. The monitoring team is comprised of a core group with additional members selected as appropriate to the area under investigation, size and complexity of the study and level of risk.

3.4. Nurses, and Clinical Research Associates/Fellows may be selected and assigned as needed.

3.5. **Conflict of interest**

It is recognized that an institutional monitoring system must utilize its own faculty and research staff members to enable the system to function. Inherent in this system is the potential for a conflict of interest to exist. Even members of the core monitoring team may have a relationship with the study to be audited. Examples of indirect relationships would include staff members who are involved in the study's HEC reports, drug dispensing, and research laboratory procedures. Direct relationships would include any physician who is a sub investigator on the study; a radiologist responsible for determining tumor measurements (even though blinded) on the subject patients; CRAs or CRNs involved in study conduct, data management or consenting of patients; a statistician involved in the data analysis for the subject study; and any individual who is supported by the grant supporting the subject study. No one is allowed to serve on a monitoring team with an indirect or direct relationship, as previously defined, to the subject study.

3.6. **Meetings.** Data and Safety Monitoring Subcommittee will meet on the first Friday of every month at 9.00 a.m. Incase the day is a public holiday, an alternate date and time will be decided.

3.7. **Administrative coordination.** The Secretary to the Subcommittee and is responsible for coordinating all meetings, monitoring visits, monitoring reports, and communications with the HEC. All records of the Subcommittee are maintained in the CRS.

4. Scientific Monitoring Procedures

4.1. Administrative Monitoring (all clinical trials)

All cancer-related clinical trials (treatment or non-treatment, regardless of sponsorship) must have the approval of the HSRC before the HEC will grant approval or approval to renew the study (annually). All clinical trials as defined undergo compliance monitoring through this system.

4.2. Institutional (Investigator-initiated) Clinical Trial Monitoring

4.2.1. **Scientific progress and accrual:**

4.2.1.1. All institutional clinical trials are monitored yearly for scientific progress, accrual, and HEC compliance. The Monitoring form (Appendix II) is completed on each study being reviewed for scientific progress. HEC compliance is reviewed and summarized and accrual is reported. These reports are then reviewed at the next meeting of the Data and Safety Monitoring Subcommittee for any necessary actions.

4.2.1.2. The Data and Safety Monitoring Subcommittee reviews (each study on an individual basis) accrual rate forecast relative to the characteristics of the study participants and estimated duration of the study. The general principles followed by the Scientific Monitoring Subcommittee in its recommendations regarding scientific progress and accruals are as follows:

4.2.2. **Underaccrual**.

4.2.2.1. At the end of the first year following activation, the Scientific Monitoring Subcommittee reviews accrual to the study. Based on the Principal Investigator's accrual forecast, if there is less than 25% of the accrual projected, a letter to the investigator would call attention to the original projection and remind the investigator that the accrual is being monitored. Accrual and scientific progress are reviewed yearly thereafter and if accrual continues to lag behind the predicted rate, the study is placed on probation unless there are extenuating circumstances and the investigator is asked to justify continuing the study. These responses are taken into consideration on an individual basis. If no accrual has taken place after 2-3 years, termination of the study is recommended.

4.2.2.2. Letters to investigators are intended to alert them to low accrual situations and offer constructive suggestions as to how to improve accrual. These might include altering the design or eligibility criteria, seeking extramural funding, activating the study at affiliate centers or through the outreach network, etc.

4.2.2.3. The Data and Safety Monitoring Subcommittee regards a situation of zero accrual as a potentially fatally flawed study. In this situation, the above rules may be adjusted and a recommendation for closure made at year two.

4.2.3. **Stopping rules.**

4.2.3.1. At the time of annual review, any early stopping rules for toxicity or response analysis described in the statistical section of the clinical trial are also reviewed to determine if a data review point has been reached. The investigator is asked to provide the Data and Safety Monitoring Subcommittee with an update on the status if accrual has reached that point. This is also scrutinized during on-site reviews.

4.2.4. **Overaccrual**.

4.2.4.1. Overaccrual within the range of 10-15% is not a deficiency. However, beyond that, assessment of reasons required.

4.3. Level of Monitoring

4.3.1. Determination of level of monitoring: At the time of initial review of the institutional clinical trial by the HSRC, a determination of the degree of monitoring is made commensurate with the phase, endpoints, level of intervention, degree of risk, size (single site vs. multiple sites) and complexity of the trial.

4.3.2. At the time of initial review, the clinical trial is reviewed to ensure that the following are adequately addressed:

- Procedures to ensure the safety of subjects in accord with the degree of risk.
- Validity and integrity of the data (an adequate biostatistical design must be present and procedures to ensure adequate data capture and how the data will be evaluated).
- Expected duration of the study based on a realistic predicted enrollment rate based on the characteristics of the participants.
- Data management systems that will ensure subjects' eligibility for the trial and data completeness and for multiple-site studies, an operational plan (i.e. eligibility checklist and data collections forms).

- Adverse event reporting (to the HSRC, HEC, funding agency, sponsor and test agent)

If any of the above areas are not adequately addressed, they required modifications are made with approval subject to their inclusion.

4.3.2.1. For studies proposing enrollment at multiple sites, the application will be required to state a plan of organization (i.e. if dose escalation is involved, how this will be managed operationally). Investigators will be asked to describe a central reporting entity that will be responsible for preparing timely summary reports of adverse events for distribution among sites and their IRB/HECs.

4.3.2.2. The frequency of the summary reports will depend on the nature of the trials. If it is later observed at the time of on-site monitoring reviews that a trial has evolved from a single site to a multiple site study, the investigator will be asked to provide a description of the operational plan as a condition of the audit.

4.3.3. In determining the level of monitoring, a study is first categorized into one of the following classes:

- Therapeutic intervention
- Non-therapeutic intervention
- Non-therapeutic, non-physical intervention

4.3.4. Therapeutic Intervention studies:

These are institutional clinical trials proposing any form of treatment of a cancer-patient population. This includes all primary forms of anti-neoplastic therapy (chemical, biological, internal and external radiation, surgery) and also includes all forms of supportive treatments, prophylactic or otherwise (hematologic growth factor support, anti-infectives, anti-fungals, narcotics, etc).

4.3.4.1. All treatment studies (phase I and II) undergo on-site case monitoring after the first three patients have been enrolled and treated.

4.3.4.2. In its initial review of the clinical trial, the Data and Safety Monitoring Subcommittee determines if the minimum level of monitoring is adequate. If it determines that a more rigorous monitoring plan is required, a plan specific to the clinical trial will be determined and its details conveyed to the principal investigator and HEC at the time of initial review.

4.3.4.3. Pivotal to this determination is the phase of the study. Since the level of risk is usually significantly higher in Phase I and pilot studies, the level of monitoring is commensurate with this. Reviews would be triggered by accrual based on the anticipated level of risk, but if in their monthly review

of adverse events for all institutional clinical trials it became apparent to the subcommittee that toxicity was higher than anticipated, intervening actions would be taken.

4.3.4.4. If the study contains a primary response endpoint, response evaluations by the investigator will be reviewed on a selected case sample.

4.3.4.5. The minimum level of monitoring for institutional treatment studies is the initial monitoring review (described above) followed by repeat on-site monitoring based on the findings for the initial review. If the Data Mionitoring and Safety Subcommittee rate the review “satisfactory”, the study is subsequently reviewed annually for scientific progress and accrual. On-site case reviews are not routinely repeated. In reviewing these studies annually, the progress report is reviewed and if the Scientific Monitoring Subcommittee notes anything in the annual report that would warrant an on-site review (such as a concerning volume/severity of adverse events), a monitoring visit will be scheduled and a case sample selected at random for review. Subsequent remonitoring would be based on those findings.

4.3.4.6. Studies are automatically scheduled for re-monitoring if the initial review is rated anything less than satisfactory (marginal, unsatisfactory). Each study and its review findings are judged on a case-by-case basis and follow-up actions are taken in accord with the type and degree of the deviations or violations, and the investigator’s response in terms of corrective actions. The norm is to re-review the study after 3-5 additional patients have been enrolled. At that time, if a corrective plan of action has been proposed its impact will be assessed.

4.3.5. Non-therapeutic intervention studies:

These clinical trials do not involve treatment of human subjects, but involve a physical intervention. There may be some degree of invasiveness, but the risk must be significantly less than that imposed in therapeutic trials.

Because there is no therapeutic intent, these studies are closely scrutinized since there may be no overt benefit to human subjects from participation. Examples are diagnostic clinical trials involving radiology, biopsy, endoscopy, phlebotomy, tumor oxygenation studies, normal wound healing, biological sample collection for laboratory correlates, and radiation treatment planning. Because of their variability, these studies are treated on a case-by-case basis in determining the degree and frequency of monitoring. Essential to this determination is the level of risk imposed weighed against potential benefits.

4.3.5.1. Non-therapeutic intervention studies are reviewed initially by the Data and Safety Monitoring Subcommittee. As for therapeutic studies, each new proposal will be assigned a level of monitoring based on the degree of risk, complexity, and nature of the trial at the time it is initially reviewed.

4.3.5.2. Studies in this category may undergo the same minimal level of monitoring as for therapeutic studies (initial on-site monitoring after first 3 patients enrolled; remonitoring based on findings).

4.3.5.3. If a study involves only minimal risk (e.g. phlebotomy only), no on-site case monitoring would necessarily be done.

4.3.6. Non-therapeutic, non-physical intervention studies:

Studies in this category involve no physical intervention. Research of this type includes cancer control investigations, quality-of-life inventories, epidemiology research, smoking cessation, cancer risk assessment, and use of excess discarded tissue.

4.3.6.1. Studies in this category are reviewed annually for scientific progress and HEC compliance.

4.3.6.2. Because this type of research does not involve any physical intervention, no on-site case monitoring is done routinely.

4.3.6.3. If a study in this category imposes the potential for untoward psychological reactions due to the area under investigation or the type of disease being investigated, or there are factors of a sensitive nature that are felt to require surveillance, Data and Safety Monitoring Subcommittee may decide to perform some form of monitoring beyond the annual progress review.

5. On-Site Case Monitoring Procedures

On-site case monitoring is done in accord with the monitoring plan determined upon initial review of the clinical trial. If a study is monitored initially after the enrollment of the first 3 subjects and the findings are less than satisfactory, Data and Safety Monitoring Subcommittee will determine when to remonitor the study based on the accrual of additional subjects.

5.1. Case sample.

Once a clinical trial is identified for monitoring, the Secretariat will forward the monitoring form to the monitoring team.

5.2. Notification.

5.2.1. The principal investigator and study coordinators of the study being monitored will be given written notification that the clinical trial will be monitored.

The Monitoring Team contacts them to arrange a convenient time for the visit by the Monitoring Team.

5.2.2. The investigator and the research staff are responsible for gathering all materials germane to the review - medical records, case reports forms, office and research records.

5.2.3. If other centers are enrolling subjects, materials needed for the review from the outside centers must be provided to the Monitoring Team. The investigator is advised that the assessment will be based on the materials present at the time.

5.3. Monitoring Team visit.

5.3.1. Prior to the onsite visit, the monitoring team will review the clinical trial to determine if the study has met a data review point so that this can be addressed at the time of the visit. The team reviews the adverse event files to determine what has already been filed on the study.

5.3.2. The monitoring team uses the primary medical record as the central document. The primary source documents are checked to ensure that subjects were not treated on clinical trial prior to final HEC approval, informed consent was properly obtained and executed, and pre-therapy requirements, eligibility criteria, treatment delivery, and adverse event reporting are in accordance with the clinical trial.

5.3.3. The clinical trial staff is interviewed to ascertain their data management systems and whether subjects are being enrolled off-site. The required materials are obtained from the sites and provided to the Monitoring Team.

5.3.4. Following the on-site visit, the Team completes the Monitoring Form. These are presented to the Data and Safety Monitoring Subcommittee. These forms describe HEC compliance, consent, accrual, study endpoints, data management systems, AE reporting, and the findings regarding subject eligibility and treatment delivery. Any areas where there does not appear to be satisfactory compliance are noted.

6. Data and Safety Monitoring Subcommittee Ratings and Recommendations

6.1. The findings of the monitoring team are reviewed and discussed by the full Data and Safety Monitoring Subcommittee.

6.2. The overall rating given to a study is a composite of scientific progress, accrual, and the onsite-monitoring findings of the conduct of the study.

6.3. If a study were found to have no deficiencies in its conduct, but was seriously lagging in accrual or violating its stopping rules, the rating would reflect the latter, and be unsatisfactory or marginal, depending on the level of deficiency in the latter areas.

6.4. In rating the conduct of the study, the Data and Safety Monitoring Subcommittee categorizes deviations as "MAJOR" or "MINOR". The Data and Safety Monitoring

Subcommittee exercises reasonable judgment in determining if a deviation should be considered major or minor.

6.4.1. Major deviations would be those variances from clinical trial specified criteria or procedures that make the resulting data questionable. Examples of these would be findings that render the subject ineligible, failure to meet regulatory requirements (including failure to document properly obtained informed consent or not obtain properly executed informed consent prior to the start of treatment), failure to comply with HEC approval and/or re-approval guidelines, treatment deviations (substantial alternation or modifications of doses not in agreement with the clinical trial specifications), and poor general data quality.

6.4.2. Minor deviations would be those that do not affect the outcome or interpretation of the study and are not described above as major deviations. For example, if a hematology value were within a small percentage of variance from the requirement, this would be categorized as a minor deviation. A significant variance from a required measure of cardiac function, such as a MUGA, would be considered major. An unacceptable frequency of minor deviations will be treated as a major deviation.

6.5. **Verification of adverse drug reaction (ADR) reporting**:

All new clinical trials are required to contain a description of procedures for adverse event reporting at the time they are reviewed by the HSRC. Depending on the type of intervention proposed, the clinical trial must contain a grading system for adverse events (i.e. Common Toxicity Criteria), reference the reporting forms to be used (investigational vs. non-investigational drug reporting), and describe oversight by the investigator for grading and attribution to the study intervention.

7. SAEs reporting procedures

7.1. Sponsored multicentric Clinical Trials

A two member SAE monitoring team will review all the reports received during the preceding month and compile data into a central database. The team also reviews the AE reports for appropriate reporting to the HEC (serious adverse events and unexpected events). This review also enables consistency of grading to occur.

7.2. Institutional clinical trials

A two member team in rotation will review the SAEs reported from these trials and will forward their recommendations to the HEC and PI within 72 hours of receiving the report.

7.3. The investigator is responsible for submission of adverse event reports to all agencies described in the clinical trial (as appropriate to the test agent and trial). These would include the pharmaceutical sponsor, and/or FDA. Information on reporting requirements is periodically distributed to all clinical investigators.

7.4. The SAE Monitoring Team compiles a monthly summary report to the subcommittee depicting all adverse events that have occurred during the preceding month for TMH (and affiliate) patients enrolled on institutional clinical trials. This report is reviewed by the Data and Safety Monitoring Subcommittee and appropriate actions taken if the volume or severity of adverse events for a particular intervention or compound appears concerning.

7.5. During monitoring visits, if serious SAEs are found which have not been appropriately reported, the Data and Safety Monitoring Subcommittee will evaluate the number and severity of the SAEs and this will be taken into account in the overall rating.

8. Review Ratings

8.1. The following guidelines are used in determining an overall rating:

- Satisfactory. No major deviations.
- Marginal. One major deviation.
- Unsatisfactory. Two major deviations.

8.2. Actions Based on Rating

8.2.1. The Data and Safety Monitoring Subcommittee determines the overall rating in accordance with the above guidelines, which is conveyed to the investigator by letter.

8.2.2. If a study receives a satisfactory rating, it will thereafter be reviewed for scientific progress and accrual annually as long as it is active, but full monitoring is not repeated.

8.2.3. Studies rated less than satisfactory are each judged individually and follow-up actions are taken in accordance with the type and degree of the deviations and/or violations.

8.2.4. Depending on the nature of the findings and the investigator's response, early re-review will be decided on a case-by-case basis at the discretion of the Data and Safety Monitoring Subcommittee. For example, if a corrective plan is proposed by the investigator, this may warrant an early re-review to determine its impact. If the only issue is underaccrual, the recommendation will follow the guidelines described above. If the case review reveals problems with eligibility, a repeat on-site visit would be conducted after a specified number of subjects have been enrolled (usually 3). The Data and Safety Monitoring Subcommittee may elect to recommend probation, suspension or termination of the clinical trial if the level of unacceptability warrants it.

8.2.5. The investigator also receives a copy of the summary monitoring report. The cover letter, summary report, and investigator's response are copied to the Chairman of the HEC.

8.3. Recommendation of Clinical Trial Suspension or Termination

8.3.1. Grounds for recommending suspension or termination of a clinical trial to the HEC include, but are not limited to:

- Zero accrual for 1-2 years or long-term low accrual.
- Stopping rule violations.
- Major violations in the conduct of the study (including serious HEC violations) that result in an unacceptable audit rating.

8.3.2. The decision to recommend suspension or termination of a clinical trial is carefully considered and takes into account whether corrective actions had been requested at previous reviews and were not implemented.

8.3.2.1. If the decision is made to recommend suspension or termination of a clinical trial, the recommendation will be made in a letter to the investigator. A letter will be sent simultaneously recommending suspension or termination of the clinical trial to the Chair of the HEC.

8.3.2.2. The TMC HEC has the ultimate authority to effect termination or suspension of a clinical trial.

8.4. Internal and External Reporting of Data and Safety Monitoring Subcommittee Findings

8.4.1. Internal Reporting:

Summary Monitoring Reports, all correspondence with principal investigators, including the Data and Safety Monitoring Subcommittee's final recommendations concerning re-review or corrective plans needed, are sent to the Chairperson of the HEC. Any correspondence and recommendations stemming from administrative monitoring findings and accrual review will also be sent to the HEC Chairperson.

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