WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

Data and Safety Monitoring Plan

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Abbreviations

AE – Adverse Event

CAP – Corrective Action Plan

CR – Complete Response

CRO – Clinical Research Organization

CTEP – Cancer Therapy Evaluation Program

CTEP-AERS - CTEP Adverse Event Reporting System

CTRU – Clinical Trials Research Unit

CTWG – Clinical Trials Working Group

DSMB – Data and Safety Monitoring Board

DSMP – Data and Safety Monitoring Plan

DSTC – Data Safety and Toxicity Committee

eCRF – electronic Case Report Forms

FDA – Food and Drug Administration

GCP – Good Clinical Practice

IDE – Investigational Device Exemption

IND – Investigational New Drug

IRB – Institutional Review Board

MBRCC – Mary Babb Randolph Cancer Center

NCI – National Cancer Institute

PI – Principal Investigator

PR – Partial Response

PRMC – Protocol Review and Monitoring Committee

PSR – Protocol Summary Reports

QA – Quality Assurance

RR – Response Review

SAE – Serious Adverse Event

SoD – School of Dentistry

SoM – School of Medicine

SoP – School of Pharmacy

SoPH – School of Public Health

UPIRTSO – Unanticipated Problem Involving Risks to Subjects or Others

WVU – West Virginia University

WVUM – WVU Medicine

I. Overview

All aspects of non-externally reviewed studies conducted by the Mary Babb Randolph Cancer Center (MBRCC) are thoroughly reviewed prior to initiation to evaluate and approve proposed data and safety monitoring plans and are continuously monitored for patient safety, to ensure the veracity of the data, and effective implementation.

Other studies conducted at the MBRCC are reviewed to confirm that the elements required to assure patient safety are present in the study protocol and carried out accordingly.

The MBRCC Data and Safety Monitoring Plan (DSMP) outlines our commitment to human subject protections in clinical trials at this institution. It is the framework for ensuring that all clinical trials conducted by the MBRCC adhere to the appropriate regulations and policies established by federal and local authorities. The DSMP serves as guidance for administration, investigators and research teams working to develop, conduct and monitor scientifically sound clinical trials while optimizing human subject research protection. The committees described in this document (further defined in the MBRCC Blue Book) ensure that the DSMP is implemented and maintained for all clinical trials.

The Clinical Trials Working Group (CTWG) is an executive committee composed of MBRCC leaders which provide administrative oversight of clinical research conducted at the MBRCC. The Protocol Review and Monitoring Committee (PRMC) is responsible for reviewing all new clinical trials; whereas the Data Safety and Toxicity Committee (DSTC) is responsible for safety, validity of data, toxicity and response reporting and monitoring of MBRCC clinical research.

A. Clinical Trials Working Group (CTWG)

This working group insures that all aspects of the clinical research process at the MBRCC are conducted according to prescribed standard operating procedures. The working group:

1. Reviews and approves all MBRCC policies and procedures related to clinical research.
2. Appoints membership and defines responsibility of the PRMC and the DSTC.
3. Serves as the review body for the PRMC and the DSTC.
4. Makes recommendations to the MBRCC Senior Leadership for assignment of MBRCC and other shared resource support.

Members of the CTWG are appointed by the MBRCC Director. Their term is co-terminus with their leadership role. The CTWG meets once a month. Ad hoc meetings to address specific

issues that require immediate attention are scheduled to insure patient safety. The current CTWG Membership listing is maintained in the Clinical Trials Operations Manual (the Blue Book).

B. Protocol Review and Monitoring Committee

The CTWG delegates the responsibility for the evaluation of data and safety monitoring plans and the determination of potential conflicts of interest for all clinical research performed at the MBRCC to the PRMC. Consistent with such the PRMC will be responsible for the following functions:

1. Reviews all new clinical trials for scientific merit, priorities and resource allocation.
2. Performs a risk assessment on all new protocols and assigns a risk level accordingly.
3. Assesses adequacy of data and safety monitoring plans for each protocol in relation to the risk assessment and in consideration of established data and safety monitoring plans per the trial sponsor.
4. Identifies potential conflict of interest in any MBRCC clinical trial.
5. Affirms relevance of the proposed clinical trial to the mission of the MBRCC.
6. Reviews quality control and safety reports submitted by the DSTC; receives and votes to accept DSTC recommendation(s) for corrective action.
7. Reviews adequacy of plans for data storage and security for non-externally reviewed clinical trials that do not require use of the OnCore® Database.
8. Reviews all ongoing clinical trials for scientific progress.
9. Oversees closure of trials for insufficient progress, prioritization changes, and quality and/or safety issues.

Members are appointed by the CTWG. Membership duration is flexible to maintain required depth and breadth of expertise related to the spectrum of clinical research conducted at the MBRCC. This committee meets twice a month. Present PRMC membership is listed on the CTRU website PRMC Members Roster.

C. Data Safety and Toxicity Committee (DSTC)

The CTWG delegates responsibility for continued review and monitoring of all clinical trials conducted by the MBRCC to the DSTC. This committee provides oversight of study progress and safety by review of accrual and adverse events at monthly meetings. The Committee:

1. Reviews all non-externally reviewed clinical trials and other trials, as appropriate, conducted at the MBRCC for progress and safety.

2. Reviews all adverse events requiring **expedited** reporting as defined in the protocol. In addition, the DSTC will review any adverse events that are considered excessive, any unexpected trending and/or any other issue deemed significant by a member of the research team.
3. Reviews reports generated by the MBRCC data quality control review process (Quality Assurance audits and response review) described in Section IV of this document.
4. Submits recommendations for corrective actions to the PRMC. The PRMC will notify the Principal Investigator of the recommended action(s).
5. Reviews major protocol violations and Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs), as defined by WVU IRB policy.
6. Confirms notifications to external sites participating in multiple-institutional clinical trials coordinated by the MBRCC of expedited adverse events and/or committee recommendations.
7. Reviews all NCI generated action letters.

Members are appointed by the CTWG. Membership duration is flexible to maintain required depth and breadth of expertise related to the spectrum of clinical research conducted at the Cancer Center. The DSTC meets once a month or interim meetings are scheduled to address specific issues that require immediate attention to insure patient safety. Present membership is listed on the CTRU website DSTC Members Roster.

DSTC Reviews and Quality Control Issues

All quality control audits and reviews are reported to the DSTC. Quality Control reviews are coordinated by the Quality Assurance (QA) Specialist of the Clinical Trials Research Unit (CTRU). Typically reports are received by the DSTC for Quality Assurance Audits, Response Reviews, Protocol Summary Reports and all other types of routine data monitoring reports. Subject confidentiality is upheld in all quality assurance reporting. These quality control reviews are described in the sections that follow. The DSTC reviews the quality control reports, ascertains if further information is required from the investigator and makes a recommendation for follow-up action if it is warranted. These decisions and recommendations are referred to the PRMC. The DSTC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., National Cancer Institute Program Director, Industry Sponsor Medical Monitor, NCTN Study Chair, etc.) and other appropriate agencies.

II. Guidelines for Protocol Data and Safety Monitoring Implementation

All clinical trials conducted at the Cancer Center must have a satisfactory data and safety monitoring plan (DSMP) that is described in detail in the protocol. The PRMC review ensures

that the degree and frequency of data and safety monitoring for individual studies will be commensurate with size, complexity and risks of the trial.

Non-externally reviewed studies are those studies led by MBRCC investigators for which there is one review body (i.e. classic investigator-initiated studies).

External-reviewed studies include all other studies that have an external agency that monitors the safety of a given trial (e.g. Cancer Therapy Evaluation Program, NCTN, and/or pharmaceutical-sponsored trials). In these instances, a protocol-specific DSMP procedure is outlined in the protocol. However, patients enrolled at MBRCC on these trials may experience serious or unexpected SAEs and these must be reported to and reviewed by the DSTC and IRB, if applicable. This is to further ensure the safety of MBRCC patients enrolled on these studies.

A. Required Elements of a Protocol Data and Safety Monitoring Plan

1. Delineation of oversight responsibilities *(e.g. external DSMB or MBRCC DSTC)*
2. Description of data and safety review process
3. Time table for submission of data, safety, and progress information to the external DSMB or DSTC, the IRB, and the sponsor.
4. Process to implement closure or suspension of studies when significant risks or benefits are identified.
5. Description of adverse event reporting procedures.

B. Oversight Responsibilities

Possible entities engaged in clinical trials data and safety oversight include:

1. DSTC
2. External DSMB
3. Patient Protocol Review Committees
    a. Early Phase I/II Patient Protocol Review Committee – This Committee reviews all active patients on Phase I and select Phase II trials and evaluates laboratory and clinical data regarding toxicity, response (if applicable) and drug tolerance (dose finding).
    b. Hematological Malignancy/Stem Cell – This Committee reviews all patients active on stem cell transplant and acute leukemia protocols and evaluates laboratory and clinical data regarding toxicity, response, and drug tolerance.
    c. Gene therapy – Patients are presented at either an ad hoc special committee or committee listed above, as deemed appropriate for the protocol.
    d. Population Science and Bio behavioral Research Review Committee

C. Protocol Risk Assessment

The PRMC is charged with assigning a risk level to each clinical trial as it pertains to patient safety at WVU. Clinical trials with an external DSMB or defined data and safety monitoring plan (i.e. external-reviewed studies) will be reviewed annually as outlined for low-risk trials, unless determined otherwise by the PRMC. Risk levels are assigned using the following scale:

1. **High Risk** – A trial may be considered high risk based on novelty of therapeutic intervention or the degree of risk to the patient. Examples include but are not limited to the following: investigator-initiated Phase I trials, first in human trials, gene therapy or any study involving drugs with potentially severe and/or life threatening side-effects (e.g., stem cell therapies).

   Investigators and the Clinical Trials Research Unit (CTRU) staff will conduct continuous review of data and patient safety with the designated Patient Protocol Review Committee (as listed in Section B above) at their weekly meeting. The status and results of each patient's treatment are discussed and documented in the minutes. The discussion will include for each dose level: the number of patients, (including those in screening, follow up and off study) significant toxicities as described in the protocol, dose adjustments, and responses observed, evaluation and approval if any planned dose level escalation or de-escalation.

   Monthly summaries will be submitted to the DSTC for review.

2. **Moderate Risk** – A moderate risk trial may include an agent with less novelty for which there is some clinical experience and appreciation of clinical toxicity. Examples include but are not limited to: Phase I, Phase II, or Phase III trials that involve an agent that has moderate toxicity.

   Quarterly summaries will be submitted to the DSTC for review.

3. **Low Risk** – A low-risk trial typically include agents for which the clinical safety spectrum is generally well characterized or other non-interventional types of studies. Examples include but are not limited to: Phase III trials with existing extensive safety data, registries, correlative trials, behavioral health, prevention, etc.

   Annual summaries are reviewed coinciding with the WVU IRB Continuing Review schedule.

The DSTC will review all major protocol violations and SAE's requiring expedited reporting, as defined in the protocol. Periodic reporting to the DSTC should include summary data regarding enrollment, patient status, and safety and toxicity as defined in Reporting Requirements (C).

Further elements of risk to consider include: conflict of interest, faculty held IND/IDE, multi-site trial, etc. The Quality Assurance Specialist will review each protocol's DSMP and report to the PRMC on its adequacy.

III. Reporting Requirements

A. Serious Adverse Events – Internally Reviewed Trials

1. Serious Adverse Events requiring expedited reporting – Reported within 24 hours

Serious Adverse Events (SAE) requiring expedited reporting within 24 hours (as described in the protocol) will also be reported to the Medical Director for Clinical Trials or DSTC Chair/Co-Chair, as defined in the protocol within one working day. CTEP AERS form or FDA MedWatch Form #3500 and/or any other documentation should be submitted per sponsor requirements. Within 5 working days the initial report and all subsequent SAE documentation that is available will be submitted to the DSTC. The DSTC will determine if further action is required.

If the SAE occurs on a multiple-institutional clinical trial coordinated by WVU MBRCC, the Network Coordinator will ensure that all participating sites are notified of the event and resulting action within two working days of the determination.

2. Serious Adverse Event – Reported within 5 working Days

Serious Adverse Events requiring expedited reporting within 5 working days (as described in the protocol) will also be sent to the DSTC. The SAE report, such as CTEP AERS form or FDA MedWatch Form #3500 and/or any other documentation available at that time will be reviewed by the DSTC to determine if further action is required.

If the SAE occurs on a multiple-institutional clinical trial coordinated by the WVU MBRCC, the Network Coordinator will ensure that all participating sites are notified of the event and resulting action within one week of the determination.

B. Serious Adverse Event – Externally sponsored studies

All SAE's requiring expedited reporting, as defined in the protocol, will be reviewed by the DSTC on a schedule determined by the PRMC assigned level of risk.

C. Protocol Summary Report

Protocol Summary Reports (PSR) are required to be submitted to the DSTC commensurate with the level of risk. The PSR provides a cumulative report of serious adverse events requiring expedited reporting, as well as any protocol violations, deviations, or unanticipated problems,

toxicities and responses (for non-externally reviewed trials) that have occurred on the protocol in the time frame specified. PSRs are reviewed at each DSTC meeting.

Protocol Summary Reports enable DSTC committee members to assess whether significant benefits or risks are occurring that would determine study continuation or closure. This information is also provided by the Patient Protocol Review Committee meeting minutes, internal audit and/or response review reports. In addition, the DSTC requires the Patient Protocol Review Committee or protocol Study Chair to submit external DSMB reports or any other significant study-related information.

In the event that there is significant risk warranting study suspension or closure, the PRMC will notify the PI of the DSTC findings. The PRMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the sponsor (e.g., NCI Program Director, Industry Sponsor Medical Monitor, NCTN Chair, etc.) and other appropriate agencies.

IV. Quality Assurance

Quality assurance of clinical trials ensures that the MBRCC maintains the same high quality of data collection and protocol compliance for all clinical trials, regardless of sponsor. All quality assurance activities will uphold the protection of the rights, safety, and the well-being of clinical trials participants.

Routine reviews will serve as a mechanism of quality control for protocol compliance including adherence to the protocol, data collection, and regulatory documentation. Quality assurance audits are periodic reviews directed at the validity of the data reported for clinical trials. These reviews will ensure that all clinical trials are conducted in accordance with Good Clinical Practice (GCP). All major protocol violations from internal and external Quality assurance audits are reviewed by the DSTC.

The QA Specialist serves as the lead auditor and notifies the PI and research staff of the audit and provides them with a case list at least two weeks prior to the audit. Audit teams, consisting of a physician and varying number of independent research support staff, may be recruited. In addition, the QA Specialist provides the audit team with audit materials for preparation in advance of the audit, coordinates the exit interview, and generates the final audit report.

A. Quality Assurance Audits

1. Non-Externally Reviewed Clinical Trials

Quality assurance audits for non-externally reviewed interventional clinical trials will be determined by the level of risk assigned to the study by the PRMC. All non-externally reviewed interventional clinical trials are subject to quality assurance audits.

Recommended Quality Assurance Audit schedule:

Risk Category	Audit Schedule	% Charts	Other
High	After 1st patient and every 6 months	30% if > 12 cases	50% of cases 2-12 or all cases if < 6 cases at one year
Moderate	Annually	20%	If < 4 cases, audit all charts
Low	≤ 3 years	10%	If < 10 cases audit all charts

These audits will include (but are not limited to) the review of the informed consent process, eligibility confirmation, adherence to protocol procedures and treatment plans, pharmacy records and storage, and regulatory documentation. Data from MBRCC clinical trials quality assurance activities will be reviewed periodically to estimate the predictive probability of violations using a statistical model to determine if modification of the QA audit schedule(s) are warranted.

The QA Specialist must report any major protocol violations immediately to the DSTC which can suspend study enrollment to protect the safety of trial patients.

The DSTC is notified of the audit findings and will communicate the need for a Corrective Action Plan (CAP) within 30 days to the PI, if warranted. Proposed corrective action plans will be reviewed by the DSTC and any further recommendations for corrective action will be submitted to the PRMC. The PRMC will communicate additional requirements to the Principal Investigator. Appeals to the findings or plan of action must be submitted to the CTWG for final review and decision.

Significant findings that involve risks to subjects will be reported immediately to the WVU IRB. The PI is responsible for reporting all other findings at least annually with the IRB continuing review, or sooner as required per IRB policies for deviations and unanticipated problems.

2. NCTN Clinical Trials

NCTN clinical trials conducted at the MBRCC are subject to the external auditing policies of the respective groups, which routinely audit sites on a three-year audit cycle. These external audits must be reported to and reviewed by: the WVU Office of Research Integrity and Compliance, WVU Internal Audit, the DSTC and subsequently the PRMC.

NCTN trials are also subject to internal Quality Assurance audits that examine a percentage of active trials for each Disease Team at least annually. A goal of 10% of cases is given as a general guideline, but will be tailored to the specifics of each study

(i.e., level of experience of the investigator or enrolling clinical research coordinator, complexity of the protocol, etc.)

These audits will include (but are not limited to) the review of the informed consent process, eligibility confirmation, adherence to protocol procedures and treatment plans, pharmacy records and storage, and regulatory documentation.

The QA Specialist must report any major protocol violations immediately to the DSTC which can suspend study enrollment to protect the safety of trial patients.

The DSTC is notified of the audit findings and will communicate the need for a Corrective Action Plan (CAP) within 30 days to the PI, if warranted. Proposed corrective action plans will be reviewed by the DSTC and further recommendations for corrective action will be submitted to the PRMC. The PRMC will communicate additional requirements to the Principal Investigator. Appeals to the findings or plan of action must be submitted to the CTWG for final review and decision.

Significant findings that involve risks to subjects will be reported immediately to the WVU IRB. The PI is responsible for reporting all other findings at least annually with the IRB continuing review, or sooner as required per IRB policies for deviations and unanticipated problems.

3. Industry-sponsored Clinical Trials

Industry-sponsored clinical trials conducted at the MBRCC are subject to the external auditing or routine monitoring policies of the study sponsor or Clinical Research Organization (CRO). These studies are also subject to internal Quality Assurance audits that examine a percentage of active trials for each Disease Team, as determined by the PRMC. The resulting corrective actions from external quality assurance audits must be reported to and are reviewed by: the WVU Office of Research Integrity and Compliance, WVU Internal Audit, and the DSTC and subsequently the PRMC.

Significant findings that involve risks to subjects will be reported immediately to the WVU IRB. The PI is responsible for reporting all other findings at least annually with the IRB continuing review, or sooner as required per IRB policies for deviations and unanticipated problems.

B. Response Review

This independent response confirmation complements the Quality Assurance Review procedures at the MBRCC. A Response Review (RR) may be performed on confirmed partial responses (PR) or complete responses (CR) on any therapeutic clinical trial, regardless of sponsor. Response Reviews are mandatory for studies without an external data and safety monitoring entity. On a quarterly basis, the QA Specialist solicits from the Disease Teams all subjects cases in which a CR or a PR was recorded. The QA Specialist recruits physician reviewers with no

connection to the case under review, obtains radiological films and any other necessary documents, and schedules a location and time for the first response review to occur. Measurements and/or assessments made by the independent reviewer are documented on the Response Review form. The RR findings are reported to the DSTC. If the independent review does not concur with the reported response from the investigator, the treating physician is notified. If the treating physician does not accept the RR findings he or she may request that a second response review be performed. If the PI wishes to appeal the second review finding, the appeal is brought to the CTWG. The MBRCC Director has final authority in the appeal process.

C. Data Quality Control (OnCore® Database)

New protocols entered into the OnCore® database undergo a data review by the PRMC Coordinator to ensure all mandatory fields are completed and the data entered corresponds to the protocol documents. The study is opened to accrual only after this validation check is passed. Once the study is opened to accrual, the OnCore® Administrator performs an additional data review on the new protocol record. In addition, protocol and subject status reports are generated at least monthly and reviewed for accuracy.

The OnCore® Administrator will review all subject data (i.e. registration, status, treatment, follow-up) at least monthly to ensure that all mandatory fields are complete. Data from Serious Adverse Events (SAEs) are reviewed by the QA Specialist within 24 hours of receiving the SAE notification to ensure all mandatory fields are completed.

OnCore® eCRF data are monitored on a monthly basis utilizing the OnCore® database Data Monitoring Console to ensure all mandatory fields are entered completely, accurately, and within time requirements. This process can often identify a misunderstanding or deficiency in the protocol requirements early in the study and can improve data quality. When a query uncovers an issue which cannot be resolved among the research staff, statistician, and PI, arbitration is achieved through the CTWG.

A summary of each subject's data record is continually available to the PI, research staff, and DSTC from the OnCore® database. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.