WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

MARY BABB RANDOLPH CANCER CENTER CLINICAL TRIALS OPERATIONS MANUAL

"The Blue Book"

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Acknowledgement

The policies and procedures in the first edition of the Mary Babb Randolph Cancer Center *Clinical Trials Operations Manual* (hereafter referred to as the "Blue Book") were adapted from the clinical trials manual of the Case Comprehensive Cancer Center and University Hospitals Case Medical Center–Ireland Cancer Center, Cleveland, OH. The Mary Babb Randolph Cancer Center wishes to both acknowledge and thank the Case Comprehensive Cancer Center Clinical Trials Unit for their support and guidance as we continue to build our clinical research enterprise.

Précis There were elements in the earlier editions of the Clinical Trials Operations Manual that were in the formative phases of development as our research mission and programs continue to evolve. These elements are, however, essential and required as we fully align research policies and procedures in keeping with NCI Cancer Center Support Grant (CCSG) guidelines. The third edition included elements that have been either established or developed and this new 4th edition further defines the roles of the investigator and team members. Several examples include the re-establishment of the Clinical Trials Working Group (CTWG), Protocol Review and Monitoring Committee (PRMC) and Data Safety and Toxicity Committee (DSTC). However, those policies and procedures that are not yet mature or implemented are designated *To Be Established* or *To Be Developed* and connoted by the abbreviation of TBE and TBD respectively, in areas of the operations manual text herein. Additionally, several CTRU and scientific administrative positions are *To Be Named*, which are connoted by TBN. Subsequent editions of the Blue Book will capture these new requirements as they come online.

You will find that the fourth edition contains revised names, roles and refinement of processes. The institutional Data Safety and Monitoring Plan (DSMP) continues to evolve and is found in Appendix 1. The plan was largely based on the University of Wisconsin Comprehensive Cancer Center DSMP. We still feel this plan has many desirable elements that best conform to our clinical trials research programs and we wish to acknowledge this support.

William Petros, PharmD.
Interim Director, MBRCC
Fourth Edition, February 2016

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Introduction

The Mary Babb Randolph Cancer Center (MBRCC) clinical research program includes resources that provide protocol review and monitoring, data and safety monitoring, administrative support, data collection, biostatistical support, web-based accrual, audits, and educational programs for Cancer Center members and support staff who participate in the conduct of cancer research on human subjects.

Our goal is to provide cutting edge innovative clinical research opportunities for the benefit of cancer patients in pursuit of our mission to reduce cancer suffering and to approach a cure for cancer. To do so requires careful development, evaluation, conduct, monitoring, analysis and reporting of research on human subjects. In this endeavor, the highest priority is placed on MBRCC investigator-initiated research. MBRCC is currently an active member of the following National Clinical Trials Network (NCTN) groups; NRG Oncology, ECOG-ACRIN and COG (Children's Oncology Group). This membership allows investigators access to a portfolio of clinical trials offered through the National Cancer Institute (NCI).

This manual provides guidelines for the safe and efficient conduct of clinical research, both interventional and non-interventional clinical trials, including population-based, behavioral, prevention and control, and observational studies, starting with a description of the components of the MBRCC Protocol Review and Monitoring System (PRMS) and appropriate Shared Resources devoted to clinical trials administration and support, including descriptions of the responsibilities, jurisdiction and authority of each of these research components.

Abbreviations

AE	Adverse Event
CAP	Corrective Action Plan
Co-I	Co-Investigator
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
NCTN	National Clinical Trials Network
PI	Principal Investigator
PR	Partial Response
PRMC	Protocol Review and Monitoring Committee
PSR	Protocol Summary Report
QA	Quality Assurance
RR	Response Review
SAE	Serious Adverse Event
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. SHARED RESOURCES

A. MARY BABB RANDOLPH CANCER CENTER ADMINISTRATION

Website: www.wvucancer.org/research

The Mary Babb Randolph Cancer Center (MBRCC) is charged with oversight and facilitation in bringing innovative clinical research to the bedside of patients suffering from or at risk for cancer and population science research that is intended to prevent or reduce the burden of cancer in the immediate communities of north-central West Virginia, the State of West Virginia as a whole, neighboring counties to the north in Pennsylvania, and to the east in western Maryland. This is accomplished through the efforts of all member institutions of the Mary Babb Randolph Cancer Center and its investigators.

The administration, in its role as a coordinating and facilitating agent, will oversee and support the following processes:

- Identify and maintain a database of all approved MBRCC members (investigators).
- Serve as the conduit of information from the National Cancer Institute (NCI) or other relevant group; to, from and between members of the MBRCC as relates to information, policy, communication and integration of clinical research.
- Act as the grant administrator for National Cancer Institute grants.
- Serve as the financial accounting office for grants as institutionally appropriate.
- Negotiate and approve specific clinical trial operating budgets and contracts as institutionally appropriate.
- Serve as the intra/interagency facilitator to ensure full review and approval of clinical trial budgets (i.e., legal, pharmacy, labs, etc.).
- Develop and oversee the CTRU annual capital and operating budgets including salaries, supplies and services.
- Provide all MBRCC leadership with analysis of financial trends and needs.
- Deploy and maintain critical Information Services (IS) systems and support for a variety of clinical trials applications.
- Support dissemination of trial information to the public (i.e., ClinicalTrials.gov website, etc.) as well as respond to individual inquiries regarding trials.
- Develop, support and oversee activities that promote awareness of and accrual to trials (i.e., marketing campaigns, news releases, etc.).
- Assure that research is responsive to the health priorities of WV and facilitates adequate engagement of and partnership with communities and community members.
- Provide technical administrative support for CTRU operations (i.e., secretarial services, meeting coordination).
- Accumulate, verify and submit accrual reports to MBRCC and institutional leadership as requested.

- Collect and summarize core usage data as required for the MBRCC leadership using software responsive to and inclusive of all types of clinical and population health research.
- Advise the MBRCC leadership on clinical trial research issues of concern or importance.

B. CLINICAL TRIALS RESEARCH UNIT (CTRU)

CTRU Director: John O. Naim, Ph.D.
Interim Medical Director for Clinical Trials: Michael Craig, M.D.
Manager, Clinical Oncology Services: Anne Ness, BSN RN CCRP

The Clinical Trials Research Unit provides a centralized infrastructure (e.g. research nursing, data management, regulatory, quality assurance and financial aspects) to support investigators. These functions include:

- Review and sign-off authority for clinical trial agreements with NCI, pharmaceutical and other sponsors, including negotiation of budgets.
- Sign-off authority for activation of clinical trials prior to final approval by the Medical Director for Clinical Trials based on satisfactory completion of review and approval by the PRMC, IRB, WVU Office of Sponsored Programs (OSP), etc.
- Coordinating the logistical plan for the initiation of a protocol including identification of research tests and activities, specimen procurement and other correlative studies thru the appropriate Cancer Center and/or other institutional core facilities (e.g., Biospecimen Processing Core), and investigational pharmacy.
- Recording user activity and charges associated with clinical trials activities.
- Training and oversight of research staff including research nurse/coordinators, data managers, and regulatory support personnel.
- Facilitating investigator compliance with local IRB and federal guidelines for research on human subjects. This includes verifying investigator compliance with human subject training, maintaining current 1572 forms, and assisting investigators with documentation of compliance with institutional guidelines governing conflict of interest.
- Providing coordinating support for each of the components of the clinical research activity of the MBRCC such as scheduling meetings, recording minutes, and maintaining files regarding the status of all trials.
- Providing internal registration system(s) to all participants in clinical trials through the MBRCC including NCI, CTEP, pharmaceutical, and other sponsors as well as population health sciences, Bio-Behavioral and other non-therapeutic trials.

- Providing data collection for each sponsor or use of the institutional OnCore® database system for investigator-initiated clinical trials.
- Provide federal protocol registration and establish federal protocol identification numbers for all clinical trials conducted at the MBRCC for uniform requirements for protocol reporting.
- Developing and maintaining SOPs located in the CTRU central office.
- Assist the PI/Study Chair with identifying any potential conflict of interest (COI) by following the WVU COI policies and procedures. http://oric.research.wvu.edu/services/conflict-of-interest

C. CLINICAL TRIALS WORKING GROUP (CTWG)

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

The working group:

- Reviews and approves all MBRCC policies and procedures related to clinical research.
- Appoints membership and defines responsibility of the PRMC and the DSTC.
- Serves as the review body for the PRMC and the DSTC.
- Oversees coordination of Clinical Trials101, an educational and training session offered throughout the course of the year.
- Makes recommendations to the MBRCC senior leadership for assignment of MBRCC and other Shared Resource support.
- Serves as the Cancer Center authoritative body to resolve any potential conflicts that may arise during the conduct of our clinical trials activities. In the event a vote is needed to reconcile any matter this is done by simple majority of the members of the committee.

Members of the CTWG are appointed by the Cancer Center Director and reflect the multiple disciplines and administrative cores involved in clinical trials. Their term is co-terminus with their leadership role in the CTRU. The CTWG meets monthly with additional Ad hoc meetings to address specific issues as needed to ensure patient safety. Members are listed on page iii.

D. MBRCC CANCER CENTER COMMITTEES

Protocol Review and Monitoring Committee (PRMC)

The Protocol Review and Monitoring Committee (PRMC) is responsible for the WVU Mary Babb Randolph Cancer Center's (MBRCC) Protocol Review and Monitoring System (PRMS). The PRMC supports the clinical, basic, and population health research of the Cancer Center by providing protocol review (and associated feedback to assist in LOI and protocol development, pre-award) and study monitoring (post award). A sub-committee, Population Sciences and Bio-Behavioral Research Committee, will oversee all population health protocols and will interact directly with the PRMC.

More specifically, the Protocol Review and Monitoring Committee is charged to accomplish the following:

- To foster the development of MBRCC research protocols which address the prevention, diagnosis, and treatment of cancer and cancer risk factors and especially those that address cancer health disparities in the State of West Virginia.
- To provide MBRCC investigators with expert feedback on LOIs and protocols, as relevant to all types of research.
- To advise the MBRCC CTWG and the WVU Institutional Review Board on the scientific merit of the proposed protocols.
- To establish priority ranking for protocols within a given disease category.
- To ensure that each clinical trial or proposed study has an appropriate study design to include: objectives and rationale, drug dosing and schedule to include escalation and de-escalation, data collection, lab correlatives, and statistical considerations.
- To ensure appropriate resources are available to support proposed study.
- To ensure that the data to be collected is appropriate to the study's goals.
- To ensure community engagement and participation where appropriate and necessary.
- To monitor the progress of WVU MBRCC protocols.
- To act on reports from the Data Safety and Toxicity Committee (DSTC), Clinical Trials Working Group (CTWG) and reports from the Medical Director for Clinical Trials.
- To recommend protocol closure due to safety issues and/or lack of scientific progress.
- To perform a risk assessment and assign risk level on all new protocols.
- To assess adequacy of data safety and monitoring plan for each proposed study.
- To identify potential conflict of interest.

Details on how the PRMC enacts these charges can be found in Section II.

Cell and Gene Therapy Scientific Subcommittee

The Cell and Gene Therapy Scientific Subcommittee is a special ad hoc subcommittee, convened at the request of the PRMC, to review clinical trials in cell and gene therapy. Issues specific to this effort include preparation of DNA reagents, evaluation of preclinical models of efficacy and gene transfer, evaluation of safety issues for response to treatment, toxicity assessment and logistical issues special to the field of cell and gene therapy. For all gene therapy protocols, the subcommittee interacts with the Investigational Pharmacy, and the Biologics Safety Committee of WVU to evaluate and resolve issues of safe handling and monitoring of novel genetic therapeutics. The subcommittee membership is determined by MBRCC CTWG.

Population Science and Bio-Behavioral Research Subcommittee

The Population Sciences and Bio-Behavioral Research Sub-Committee reports all their recommendations in population health research to the PRMC for implementation through the PRMS. The Committee includes experts in public health, pharmacy, prevention, epidemiology, statistics, and policy. Community input will also be sought out as appropriate. The Committee will provide input and review regarding the objectives and rationale of the study, the study design, sample size, feasibility, and analyses.

Examples of population health research include:

- Clinical (non-pharmaceutical) and community-based intervention trials (e.g., tobacco cessation interventions)
- Evaluation studies (e.g., community-wide screening programs or media campaigns, policy assessments)
- Needs assessments (e.g., such caregiver needs or issues)
- Cost-effectiveness analyses (e.g., tx A vs. tx B)
- Compliance studies
- Determinants of health studies (e.g., GIS or other mapping of cancer clusters)
- Patterns of care and practice studies (e.g., quality of care issues)
- Service and technology utilization studies (e.g., access to care)
- Health economics & pharmaco-economics

Data Safety and Toxicity Committee (DSTC)

The DSTC is an independent committee that reports its findings to the Medical Director for Clinical Trials, who in turn reports to the IRB, the MBRCC Director, the PRMC and other reporting agencies and sponsors dictated by the particular protocol as appropriate.

The DSTC performs the following functions:

- Oversees all aspects of data, safety and monitoring for institutionally sponsored, investigator-initiated trials and, in particular, those trials that do not have external monitoring, such as those supported by NCI through R01, R21, P01, and U01 mechanisms.
- For non-investigator-initiated trials, the DSTC has oversight for all internal clinical trials patient safety, reviewing all internal deviations, SAE's and unexpected events. This also includes external events experienced by subjects enrolled at sites participating in MBRCC sponsored multicenter clinical trials.

Details on how the DSTC enacts these charges can be found in Section II.

E. COLLABORATIVE STUDIES

CTRU Director: John O. Naim, Ph.D.
CTRU Manager Clinical Oncology Services: Anne Ness, RN, BSN, CCRP
MBRCC Network Coordinator: Yvonne Shaw, MA, CCRC
Quality Assurance Specialist: Karen Stauffer, RN, CCRP

The Mary Babb Randolph Cancer Center (MBRCC) coordinates investigator-initiated, NCI sponsored NCTN trials and other sponsored trials with selected institutions. This collaboration serves several purposes: it establishes a positive working relationship with other institutions; it provides access to novel therapies and trials to residents throughout West Virginia who otherwise may not have access; and it enables the MBRCC to achieve protocol objectives in a timely manner. As the coordinating center, the MBRCC maintains the highest possible standards through oversight of data including toxicity and response, and strict adherence to Good Clinical Practice (GCP) guidance.

For investigator-initiated studies, institutions are selected at the discretion of the Mary Babb Randolph Cancer Center's Principal Investigator (PI), with approval by the sponsor as applicable. Each institution must identify a PI who will accept responsibility for the conduct of the study at his/her respective institution. See Appendix 2 Collaborating Institutions.

F. CLINICAL TRIALS INFORMATICS

OnCore®

The CTRU and MBRCC implemented OnCore® (Forte Research, Inc., Madison, WI) in December 2009 and upgraded to the Enterprise Platform in 2014. OnCore® is an enterprise class clinical and translational research software that supports patient recruitment, IRB and study monitoring, subject data collection, project planning, study design, protocol compliance, budget, invoicing, and milestone management; data safety monitoring, adverse event reporting, system integration and study execution. OnCore® is caBIG Bronze certified and 21 CFR Part 11 compliant. The outline below describes the functional features of OnCore®.

Study Administration

- Protocol Management
- Subject registration and scheduling
- Regulatory reporting (continuing reviews, FDA reporting, etc.)
- Adverse event and deviation management tracking and reporting
- Budgeting, milestones, invoice, and payment/receipts processing
- Management of research organizations, personnel, and collaborators

Clinical Data Management

- Patient Profiling
- Longitudinal, patient-level information collection and analysis
- Study-specific data collection and analysis
- Workflow configuration
- Integration with internal and third party information systems

MBRCC investigators are strongly encouraged to utilize the OnCore® database for all electronic data capture (EDC) for both treatment and non-treatment investigator initiated trials. The Database Administrator will assist investigators with development of electronic case report forms (eCRFs). OnCore® EDC capabilities allows for secure data monitoring and auditing. Once the data has been verified, it can then be downloaded into Excel or SAS for analysis.

See OnCore® Guidance Document located in the CTRU office.

Merlin: Electronic Medical Records (EMR) at WVUMedicine

An Epic EMR system called *"Merlin"* was implemented in March 2009. It is expected that all clinical observations will be noted in Merlin. On occasions when study observations are noted on paper, these documents shall be scanned and added to the patient's chart through the HPF system. The Merlin EMR system is the **only area where source documents** are located at WVUMedicine. WVUH Policies can be found at:

http://nt-intranet.wvuh.wvuhs.com:81/connect/connect_wvuh_policies.htm

Red Cap

REDCap is a secure, web-based application for building and managing online surveys and databases. REDCap's stream-lined process for rapidly developing projects, it is suited for less complex studies, and surveys. You may create and design projects using 1) the online method from your web browser using the Online Designer; and/or 2) the offline method by constructing a 'data dictionary' template file in Microsoft Excel, which can be later uploaded into REDCap.

Both surveys and databases (or a mixture of the two) can be built using these methods. REDCap can be accessed through the Clinical Translation Science Institute (CTSI) at, https://redcap.wvctsi.org/redcap/

G. CLINICAL TRIALS DISEASE TEAMS

The Clinical Trials Disease Teams consist of disease-focused clinical research investigators and biostatisticians involved in the development and review of clinical cancer protocols. Each of these teams is in different stages of evolution with the Breast and Hematological Malignancies / Stem Cell Transplant teams the most robust. Clinical Trial Disease Team meetings will be held periodically in conjunction with established Clinical Tumor Board meetings.

The Clinical Trials Disease Teams perform the following functions:

- Define the clinical research priorities for their specialty.
- Provide a mechanism for development of new protocols, emphasizing investigator-initiated research. Review all disease-specialty letters of intent (LOI).
- Develop laboratory correlative studies in collaboration with appropriate MBRCC scientific programs and scientific collaborators.
- Recommend action to the PRMC for trial advocacy, priority, extension to affiliates, marketing for accrual, and amendment review and/or other suggestions.
- Review and provide advocacy for NCTN and pharmaceutical sponsored trials to determine participation. This review should include; schema, inclusion/exclusion criteria, special procedures, and/or trial progress.
- Review and/or recommend action for protocol amendments.
- Review and/or recommend action for continuing review prior to submission to the IRB. This includes a review of accrual, toxicities, response rates, and/or continuing clinician interest.

In general, protocols are placed on the Protocol Review and Monitoring Committee agenda once the appropriate Clinical Trials Disease Team has signed off on a trial see Appendix 3 for PRMC Forms. Under rare circumstances, a protocol may be placed on a PRMC agenda prior to Disease Team signoff with the approval of the Disease Team Chair and the PRMC Chair. In the event the determination of PIs has not been made by the Clinical Trials Disease Team, this will be determined by the PRMC at the meeting at which the particular trial is being reviewed. The Disease Team Roster can be found on the CTRU website.

H. BIOSPECIMEN PROCESSING CORE (BPC) FACILITY

Facility Director: William Petros, Pharm.D.
Location(s): Rooms 1826 & 1817 MBRCC

The Biospecimen Processing Core Facility (BPC) supports Mary Babb Randolph Cancer Center clinical research trials by providing infrastructure for laboratory correlative studies. This includes sample-related activities such as acquiring, logging, collecting, tracking, processing, storage and distribution to collaborating laboratories. The BPC links to MBRCC shared resources and collaborating faculty labs for conduct of specialized assays. All data are maintained in central electronic databases.

Protocol Development

BPC personnel are available to meet with investigators during the early stages of protocol development to resolve sample related issues. The BPC can provide cost estimates to aid in budget development and detailed information about sample requirements for methods sections. The BPC also assists the PI in securing scientific collaboration(s) for the pursuit of pharmacokinetic and pharmacodynamic laboratory correlative studies to develop biomarkers of drug and target effects. This will entail collaboration(s) with Cancer Center scientists; scientists throughout the Health Sciences Center campus (e.g., Schools of Dentistry, Medicine, Nursing and Pharmacy), and with other laboratories such as the National Institute of Occupational Safety and Health (NIOSH) and schools on the undergraduate campus (e.g., School of Engineering). Appropriate budgets are developed to support this work. There are also prospects for the BPC to develop appropriate assays for laboratory correlative studies.

Sample Collection, Processing, Storage, and Distribution

Using the protocol as a guide, the BPC develops clear, concise instructions for collection, processing, and distribution of samples for laboratory correlates. Instructions are then used by research nurse/ coordinators and processing personnel. The BPC also:

- Collects, logs, and tracks samples of biospecimens, storing the information in a database available to collaborating investigators and laboratories.
- Freezes and stores samples prior to distribution to the designated laboratory.
- Distributes samples to on-campus collaborating research laboratories.
- Ships samples to off-campus collaborating or reference laboratories (Trained to ship dangerous goods pursuant to IATA and 49 CFR Part 172 regulations as well as maintaining compliance with institutional biohazard and patient confidentiality standards.)

- Coordinates with collaborating MBRCC shared resources (e.g., Flow Cytometry, Histology, Molecular Medicine, Clinical Pharmacology, etc.) for specialized expertise and services as required.
- Maintains all necessary processing equipment including centrifuges, freezers, etc.
- Coordinates with collaborating faculty laboratories in conducting specific assays.

II. PROTOCOL REVIEW AND MONITORING SYSTEMS

A. PROTOCOL REVIEW AND MONITORING COMMITTEE (PRMC)

Co-Chair: Abraham Kanate, MD
Co-Chair: Mohammed Almubarak, M.D.
PRMC Coordinator: John Naim, Ph.D., Director CTRU
PRMC Co-Coordinator: Laila Wallace, CCRP

Purpose

The Protocol Review and Monitoring Committee considers new concepts presented by individual investigators, and it reviews new protocols and amendments. The PRMC focuses on investigator-initiated therapeutic protocols; however, the PRMC reviews all cancer protocols conducted at the institutions affiliated with the Mary Babb Randolph Cancer Center, including those sponsored by the national cooperative oncology groups (administrative review) and the pharmaceutical industry (full committee review).

Emphasis is placed on review of investigator-initiated institutional trials, including population, behavioral and prevention studies. Of greatest importance is the assistance the Protocol Review and Monitoring Committee provides investigators in the development of concepts or Letters of Intent (LOIs) that lead to successful activation of novel therapeutic trials.

The Committee has sufficient breadth of expertise to allow objective and critical scientific review of all types of therapeutic and investigator-initiated clinical trials. At time of the review, a representative (preferably the PI) for the trial participates in the discussion, but is not involved in the review process itself. Often trials are conditionally approved pending clarification of certain scientific elements.

The PRMC is charged with review of the scientific rationale for the trial, establishing the priority relative to other clinical trials, in large part taking the advice of the Clinical Trials Disease Teams (especially for NCTN trials which are administratively approved by the PRMC upon recommendation by the appropriate team), and providing input and review regarding the objectives and rationale of the study, the study design including assessment of drug schedule, drug dose sequence plus escalation and de-escalation, and laboratory correlative studies,

biostatistical input of endpoints and sample size, feasibility of both accrual and patient tolerance and completion of laboratory correlative studies.

Requirement

A study must be reviewed by the PRMC in order to be listed as a MBRCC protocol. Furthermore, the WVU IRB requires that all cancer-related clinical research protocols involving human subjects and participants (including clinical, prevention, translational, population, and behavioral studies) be reviewed by the PRMC before IRB consideration (See Appendix 4).

PRMC Membership

The MBRCC Clinical Trials Working Group (CTWG) appoints members of the Protocol Review and Monitoring Committee. PRMC membership is selected to ensure diverse expertise relevant to cancer clinical research. The core membership is composed of pharmacists, nurses, clinical investigators, biostatisticians, translational scientists and patient advocates. Members are expected to participate in the committee meeting and provide focused expertise as needed in protocol review. The PRMC includes a balance of senior clinical investigators and new clinical investigators so as to foster the development of new clinical investigators. Additional reviewers are asked by the PRMC to comment on specific protocols and to assist in the review of protocols in their area of expertise. In rare instances, the PRMC may invite an outside reviewer or convene an ad hoc committee to assist with the review of a protocol or other matter that falls outside the committee's expertise or to address a scientific issue that may entail a potential conflict.

Any PRMC member with an actual or potential conflict of interest must recuse himself/herself from discussion and voting on a protocol with which he/she has a conflict.

PRMC Operations

The PRMC meets on the first and third Tuesday of each month. The meeting is chaired on a rotating basis by the one of the two Co-Chairs; each is responsible for sign-off of final minutes for the appropriate meeting chaired. The PRMC Chair is responsible for overall coordination of the meeting and responding to or directing any inquiries. The assigned meeting Chair and PRMC Coordinator develop the meeting agenda, which is distributed a minimum of 5 days before each scheduled meeting. The Committee reviews new protocols and monitors the progress of active studies. The Committee places a major emphasis on investigator-initiated clinical protocols, but reviews all clinical trials conducted at MBRCC including those sponsored by national cooperative oncology groups (upon recommendation of the Clinical Trials Disease Team) and the pharmaceutical industry.

The Role of Clinical Trials Disease Teams

Initial pre-review for all trials is undertaken by Clinical Trials Disease Teams. The teams provide pre-review by experts in their field for scientific merit, prioritization, and intent to accrue patients. Interactive Clinical Trials Disease Teams and associated co-leaders were established by the Cancer Center for directing the clinical trials research agenda for each team. The co-leaders are charged with setting a single research agenda, identifying new studies for activation, and making recommendations to the PRMC.

Requirements for Submission to Full Protocol Review

During the PRMC review process the emphasis is placed on investigator-initiated institutional trials. By the time these trials are reviewed, biostatistical input has been provided through the Biostatistics Core Facility faculty, and research nurses have participated in the logistical operations development. The Clinical Trials Disease Teams have reviewed the concept or LOI for the availability of patients and for overlap in prioritization relative to other active clinical trials. Behavioral research protocols are pre-reviewed for scientific merit by the Prevention, Control and Population Research Program leadership group.

For investigator initiated protocols submitted to the PRMC, protocol numbers are assigned via the following format.

> The protocol number has an alphanumeric designation, such as WVU020602. The alphabetical portion indicates the institution while the number indicates the sequence of protocol initiation, location of disease site or protocol type and the year during which the protocol was submitted for approval through the IRB.
>
> Disease sites/type of protocol;
>
> 01 = Breast
> 02 = GI
> 03 = CNS
> 04 = Lymphoma
> 05 = Lung
> 06 = Melanoma
> 07 = Sarcoma
> 08 = GU
> 09 = Leukemia
> 10= Supportive Care
> 11= Lab Correlate
> 12= Multiple Myeloma
> 13= Transplant
> 14= Registry/Epidemiology/Observational
> 15=Diagnostic/Screening/Early Detection
> 16= Head and Neck
>
> Therefore, WVU020615 indicates an institutional protocol (WVU) that is the second (indicated by "02") protocol for "melanoma" (indicated by "06") that was approved during the year 2015 (indicated by the "15").

The fourteen protocol sections or the equivalent referenced in Appendix 5 must be present. For investigator-initiated trials, the statistical section should be developed in consultation with a MBRCC biostatistician. Investigator-initiated protocols must be pre-reviewed by the appropriate

Scientific Disease Team and/or the following specialty committees: Stem Cell Biology and Bone Marrow Transplant Committee; and the Early Phase I/II Trials Committee. Complete and finalized protocols and their associated consent are submitted to the PRMC for review via OnCore® ePRMS. Reviewers are assigned and protocols are added to the PRMC's next available agenda.

Review of New Protocols

Prior to the meeting of the PRMC, two members are designated by the Chair and PRMC Coordinator to review each protocol, as well as a biostatistician, investigational pharmacist, and research nurse/coordinator, if supported by the CTRU. In general, the reviewers will be representative of the discipline appropriate for the protocol under review. The PRMC will make every effort to avoid assigning potential co-investigators as reviewers. The reviewers receive a complete protocol and sign-off sheet for submission to the PRMC. A PRMC submission in OnCore®, Reviewers', Statistician's, and Pharmacy Sign-Off sheets are used to facilitate the review process, see Appendix 3.

The PRMC ensures that each clinical trial has an appropriate statistical analysis section and a realistic accrual goal as well as a Data Safety and Monitoring Plan (DSMP). The protocol review statistician is responsible for the statistical review of all therapeutic or prevention trials and is responsible for the statistical sign-off required by the Mary Babb Randolph Cancer Center PRMC and the WVU Institutional Review Board. A formal statistical sign-off is required for all protocols except NCTN studies.

A protocol specific data safety monitoring plan (DSMP) must be provided and conform to the Blue Book policies and procedures. A protocol can defer to the MBRCC DSMP (Appendix 1). Elements of the protocol specific DSMP include:

- Monitoring and reporting requirements
- Adverse event reporting
- Study progress review

The PRMC evaluates the scientific merit of proposed protocols, appropriateness of the target population, risk assessment, data safety monitoring plan and the adequacy and appropriateness of patient care. The PRMC also considers the priority vis-à-vis other active protocols in the MBRCC, generally taking the recommendations of the Scientific Disease Teams and the Population Science and Behavioral Research subcommittee.

National Clinical Trials Network Protocols

NCTN trials are administratively reviewed by the PRMC. The Clinical Trials Disease Team completes the required PRMC Submission Form, the research nurse/coordinator submits the Research Coordinator sign-off document and enters the protocol into OnCore®. The protocol is

then forwarded to the investigational pharmacist for review. Once all the review forms are completed, the NCTN protocol is then reviewed by the PRMC Chair and either administratively approved or forwarded to the PRMC for full review.

Population Science and Bio-Behavioral Protocols

Population Science and Bio-Behavioral protocols are reviewed in a similar manner to therapeutic protocols by a special dedicated committee to review these types of studies under the authority of the Medical Director for Clinical Trials. This subcommittee of reviewers also includes members of the Cancer Prevention, Control and Population Research Program, in addition to members of the PRMC with content expertise in the disease or study topic. The Population Science Research Program membership has broad expertise in cancer control research. They assess the scientific merit of the non-therapeutic trial, and represent this review to the PRMC.

Review Recommendations

The PRMC may take one of the following actions on a protocol: Approved, approved pending acceptable clarification/revision, re-review required (tabled), or not approved. Action is based on the majority vote of the membership.

Written recommendations are given to investigators, and the PRMC will re-review deferred/disapproved protocols after modification; if found acceptable, the review and approval is forwarded in writing to the Principal Investigator. Using the priority score, a protocol prioritization slot and target patient accrual rate is identified following the recommendations of the Clinical Trials Disease Team leaders and entered into the database.

The PRMC is also charged with assigning a risk level to each Investigator Initiated research study using the following scale:

- High risk (e.g., gene therapy, phase I, BMT trials)
- Medium risk (e.g., Phase I/II trials with intervention of expected moderate toxicity)
- Low risk (e.g., Phase III trials with agents that have a known low-moderate toxicity)

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

Protocol Amendments

The PRMC reviews and must approve all investigator-initiated protocol changes that affect scientific goals or treatment. Specifically, this includes a change in objectives or sample collection, change in treatment/dosing, revisions to eligibility or revisions to consent form related

to significant toxicities or late effects. All major may be reviewed by the full PRMC or administratively approved by the Chair, depending on the change. Major changes in the treatment intervention, increased risk, or toxicity reporting are reviewed by the full Committee.

B. DATA SAFETY AND TOXICITY COMMITTEE

Co-Chair: Mohammed Almubarak, M.D.
Co-Chair: M. Adham Salkeni, M.D.
Committee Coordinator: Karen Stauffer, RN, CCRP

Purpose

The purpose of the Data Safety and Toxicity Committee (DSTC) is to oversee all aspects of data monitoring and safety for institutionally sponsored, investigator-initiated, and those trials that do not have external monitoring that are active at the Mary Babb Randolph Cancer Center. The DSTC meets monthly. The DSTC is an independent committee that reports its findings to the Medical Director for Clinical Trials, who in turn reports to the IRB, the Mary Babb Randolph Cancer Center Director, the Protocol Review and Monitoring Committee and other reporting agencies and sponsors dictated by the particular protocol as appropriate.

DSTC membership is determined by Mary Babb Randolph Cancer Center leadership at the recommendation of the Clinical Trials Working Group (CTWG). Membership duration is flexible to maintain required depth and breadth of expertise related to the spectrum of clinical research conducted at the MBRCC. The membership will be sufficient to allow adequate review of protocols. Principal Investigators (PIs) listed on a protocol under review will not participate in the evaluation of that protocol. It is expected that members will attend 75% of the monthly meetings yearly. Between meetings, the DSTC Committee Coordinator, Quality Assurance Specialist and/or the DSTC Chair or Co-Chair review serious toxicity reports and medical alerts that require immediate action and report this activity to the Medical Director for Clinical Trials as appropriate. When necessary, they also call special meetings and/or request directly to the Clinical Trials Working Group (CTWG) and the IRB that trials be placed on accrual hold, suspension or termination (depending on the level of concern), if there is an issue that would affect patient safety.

The DSTC performs the following functions:

- Oversees all aspects of data, safety and monitoring for institutionally sponsored trials, investigator-initiated trials and, in particular, those trials that do not have external monitoring, such as those supported by NCI through R01, R21, P01, and U01 mechanisms that do not have Theradex or other external monitoring.
- For non-investigator-initiated trials, the DSTC has oversight for all internal clinical trials

patient safety.

- The DSTC reviews SAEs in the following manner:
  - Definitions of SAEs:
    - **Internal SAEs** are those SAEs experienced by subjects enrolled in trials that are located at site(s) coordinated by the MBRCC, including collaborating sites.
    - **External SAEs** are considered those that are experienced by subjects that are enrolled in multicenter clinical trials at sites other than the site over which the MBRCC DSTC has oversight.
  - The CTRU will send the internal and external reports that meet DSTC criteria for review, to the DSTC as outlined below:
    - SAEs occurring before the first day of treatment do not require reporting to the DSTC. (There are, however, SAE reporting requirements per study guidelines if patient is registered to a trial but has not been treated. These would not be considered treatment related and therefore do not need to go to the DSTC.)
    - All internal SAEs from trials that are coordinated by the MBRCC are reviewed at the meeting following their receipt to the DSTC.
    - All SAEs from affiliate institutions of the trials that are coordinated by the MBRCC are considered by the DSTC to be internal, and are therefore reviewed at the meeting following their receipt to the DSTC.
    - External reports will be reviewed only for new and unexpected toxicities related to the investigational treatment that are on the same protocol as ones in which the MBRCC participates.
  - If immediate action is required for patient safety, the Chair or Co-Chair is advised and action is taken as appropriate.

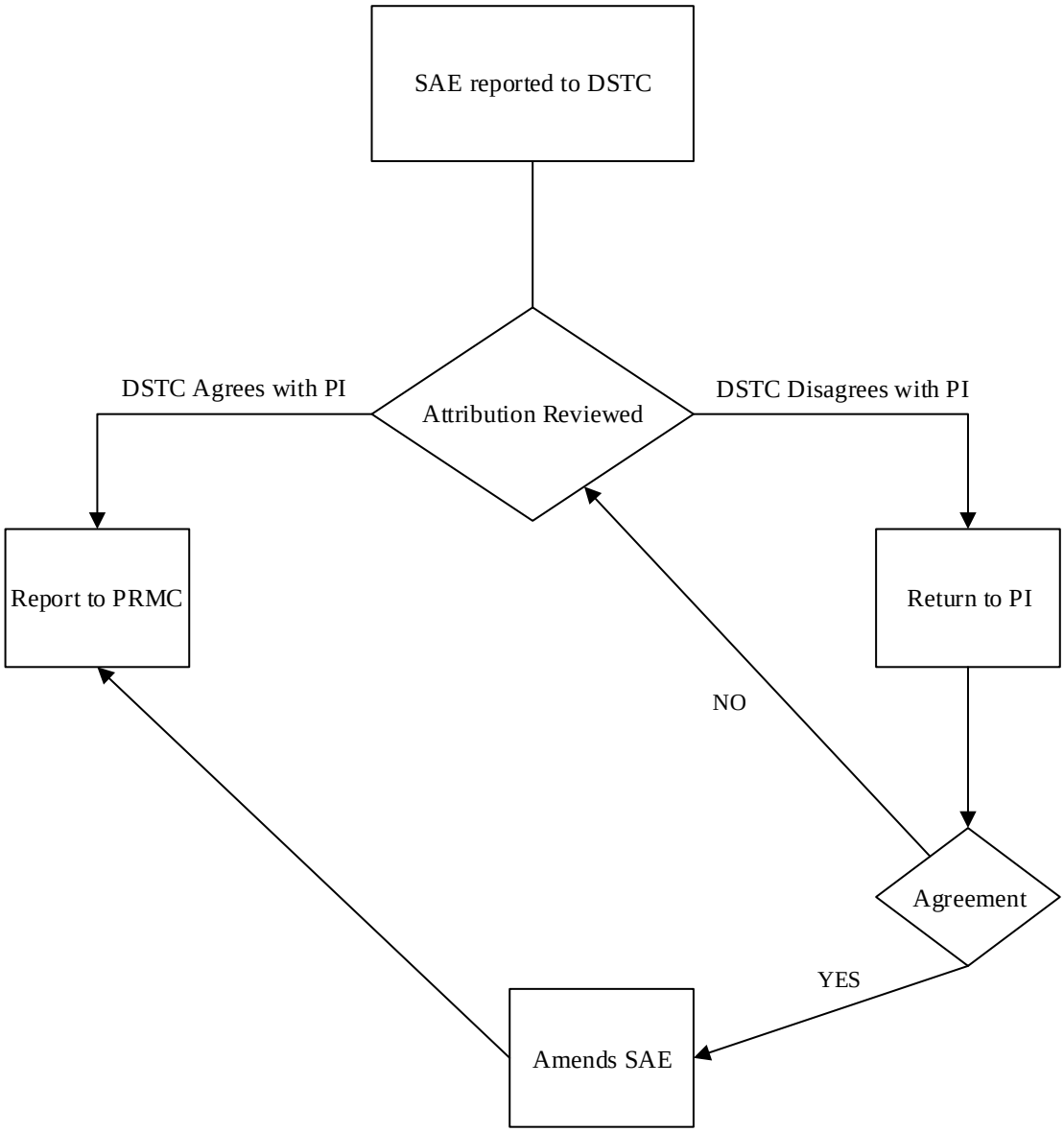
General DSTC procedures:

- Action Letters for trials coordinated by the MBRCC or that have reference to an agent being given to a patient treated at the MBRCC should be reviewed at the meeting following their receipt to the DSTC.
- It is the expectation of the DSTC that the PI will review all internal and external reports, and that the PI will provide these reports to the IRB as part of the continuing review.
- The DSTC reviews the relationship of the toxicity to the investigational agent or treatment that was assigned by the PI.
- The DSTC review determines whether the serious adverse event (SAE) requires action such as a request for more information on the SAE, or a request to the physician to consider changing the relationship of the attribution. (See algorithm for *SAE Review of Attribution* on page 22)

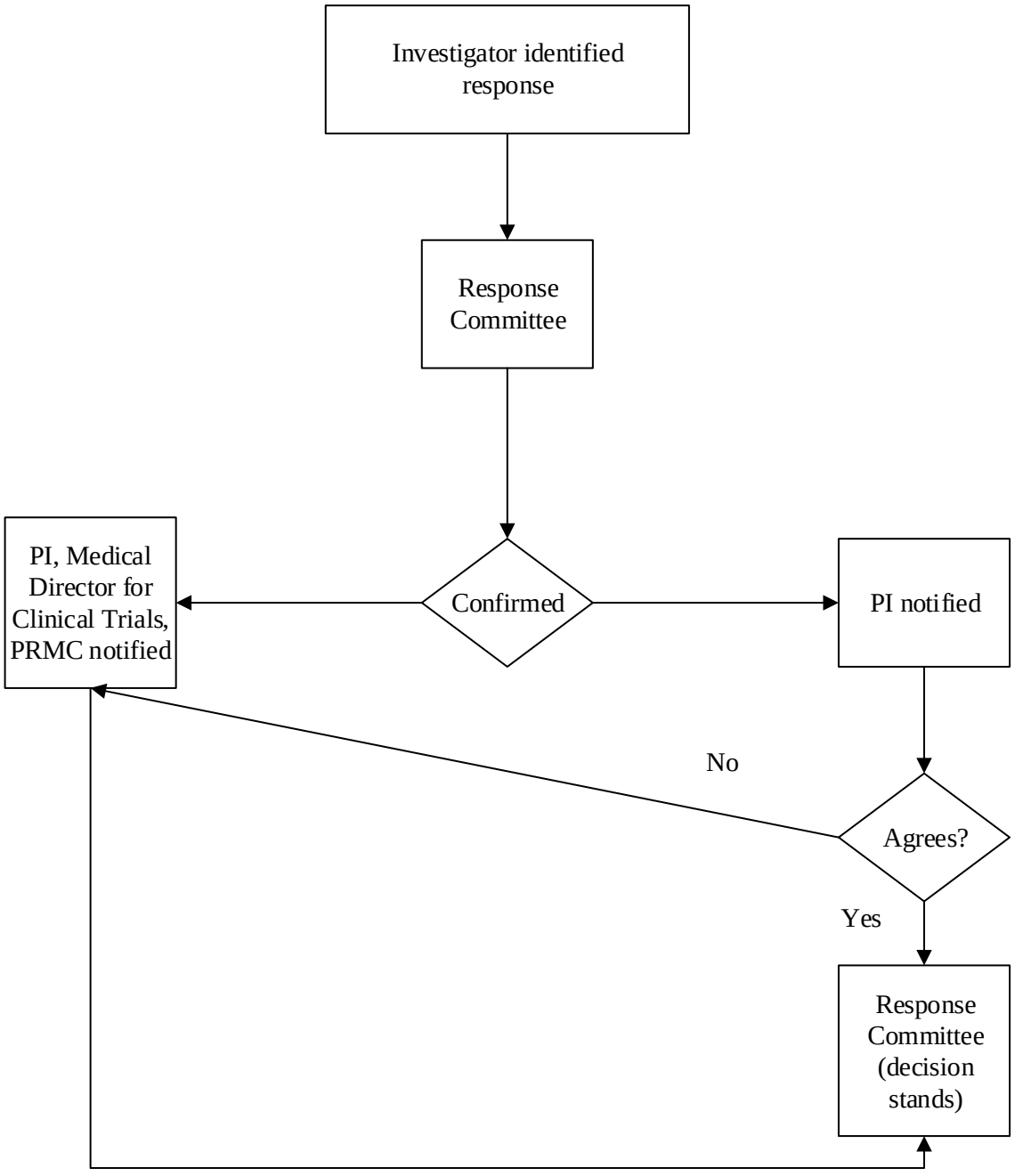
- The DSTC may make a recommendation to the Medical Director for Clinical Trials to hold accrual to the trial if an early stopping rule endpoint is reached, or to recommend closing a trial based on excessive toxicity. However, depending on the urgency of the recommendation, a committee meeting is not required for a recommendation to review the status of a protocol; a protocol recommended for suspension can be directed to the Medical Director for Clinical Trials for action. The decision to suspend or close a trial is communicated by the Medical Director for Clinical Trials to the protocol sponsor and the relevant IRB and PRMC.
- The Chair of the DSTC is empowered to immediately suspend a trial for safety considerations. The decision to suspend or close a trial is communicated to the protocol sponsor and the IRB by the PRMC on behalf of Medical Director for Clinical Trials.
- It is also required that the CTRU notifies the IRB, CTEP/NCI, FDA, and the Office of Biotechnology Affairs (for cell and gene therapy trials) of all serious safety related events that require a recommendation of protocol suspension to accrual or closure based on toxicity issues.
- The DSTC sends the meeting minutes and recommendations of the DSTC to the PRMC for its review and possible action.
- Since all protocols must contain a complete Data Safety and Monitoring Plan, in the case that the MBRCC DSTC is the designated institutional monitoring body, the DSTC will become the core review body for toxicity and data integrity for the trial. The DSTC therefore, reviews data, safety reports, adverse events and audit reports.
- When audit reports require corrective action plans, the plans are reviewed, and the DSTC determines if the proposals include measures that adequately offer education or measures that correct the deficiency and prevent future errors.
- If and when necessary, the DSTC may appoint an additional group within the institution to assist in reviewing protocol data and quality assurance.
- When appropriate, the DSTC may request a change in the consent form to inform patients of previously unrecognized risks; a change in the protocol to modify dose, schedule or toxicity of the drug or regimen; and revisions in patient monitoring as appropriate.
- Reviews protocol violations for recurring or major events: for example, ineligibility, consent form issues, treatment error or a treatment that is not within the guidelines of the protocol.
- The DSTC receives and reviews continuing review reports specifically to review accrual goals and safety. The DSTC will determine whether an early stopping toxicity endpoint has been met and whether protocol and consent form modifications are needed. DSTC reviews the IRB continuing review reports of clinical activity and outcomes for all institutional therapeutic Phase I and II trials that are open or for those that are closed but have had activity of either accrual or SAEs in the year being reported, specifically to review accrual, toxicity, response and safety. There is reconciliation of SAE reports submitted to the IRB and the DSTC. Clinical responses should only be reported in the continuing report if they have been confirmed by the DSTC. It is preferable that this submission occurs prior to IRB submission.

- Population science and/or behavioral trials will be annually reviewed by the Population Science/Behavioral Research Review Committee.
- If the Population Science/Behavioral Research Patient Review Committee believes that a trial has a safety concern/issue, this committee will refer the issue to the DSTC. All internal SAEs are to be forwarded to the DSTC.
- Reviews all submitted protocol-specific special safety reviews for selected institutional Phase I and II trials. Examples of these include novel agents, gene therapy trials, and trials of high complexity.
- Confirms independent review of all partial and complete responses of MBRCC investigator-initiated trials, and those trials for which the physician requests an unbiased review, based on the criteria for response defined in the protocol. Responses must be confirmed by the DSTC to be considered reportable. See *Validation of Response* algorithm on page 23.

Serious Adverse Event Review of Attribution



Validation of Response



C. DATA SAFETY AND MONITORING PLAN (DSMP)

All investigator-initiated protocols have in place a Data and Safety Monitoring Plan (DSMP) approved by the Cancer Center Protocol Review and Monitoring Committee (PRMC) aligned with the MBRCC institutional plan (Appendix 1), which will serve as the basis for the NCI-approved plan at time of CCSG application. The plan ensures the safety of participants, the validity of data, and the appropriate termination of studies in the event that undue risks have been uncovered, or when it appears that the trial cannot be completed successfully.

Particular attention is given to monitoring investigator-initiated clinical trials, especially those for which there is no independent outside monitoring program. The responsibility for data and safety monitoring in the Cancer Center primarily rests with the Data Safety and Toxicity Committee (DSTC).

MBRCC Shared Resources and Committees Involved in Data and Safety Monitoring

Data Safety and Toxicity Committee (DSTC): This committee is the focal point in the Cancer Center for data and safety monitoring and the central body to review serious adverse events (SAEs), externally submitted SAE reports, IRB continuing renewals including review of toxicity, confirmation of objective responses reported in investigator-initiated studies, and early stopping rule milestones as appropriate for the degree of risk in the particular clinical trial. The DSTC is described more fully in Section F below.

Clinical Trials Research Unit (CTRU): Research nurse/coordinators monitor all patients on clinical therapeutic protocols covered by the DSMP. These coordinators evaluate patients at each treatment and follow-up encounter. Toxicity is assessed and reported to the appropriate Patient Protocol Review Committee (see below). Serious adverse events (SAEs) are reported to the attending physician, the principal investigator (PI), the DSTC, IRB, and to the appropriate agency as outlined below. The CTRU performs data audits to ensure timely collection and accurate reporting of data. Accrual reports are run for quarterly and are provided to the PRMC and Clinical Trials Working Group.

Biostatistics Core Facility: This facility collects data on early stopping rules, and advises the DSTC, PRMC and Cancer Center leadership regarding trial termination for meeting accrual objectives, lack or unacceptable pace of accrual for a given trial, and for reasons of protocol-defined early stopping rules for efficacy or safety.

Patient Protocol Review Committees: The following committees review all active patients on clinical trials for patient tolerance, toxicity, SAE reports, eligibility compliance, completeness of data collection, protocol violations, and review printed data spreadsheets. Each committee is composed of the research nurse/coordinators, PIs, and attending physicians involved in patient accrual. Each committee reports pertinent findings to the DSTC. SAEs are independently reported to appropriate agencies (e.g., IRB, NCI/CTEP, NCTN, and pharmaceutical sponsor) as outlined in the DSMP.

- Early Phase I/II Patient Protocol Review Committee: This Committee reviews all active patients on Phase I trials and evaluates laboratory and clinical data regarding toxicity, response if applicable, and drug tolerance (dose finding). When necessary, the DSTC audits first patient entry into high-risk trials, including agents that are used first-time in humans. The Committee will also review active patients on Phase II trials as appropriate and according to the Data Safety Monitoring Plan approved by the PRMC. As appropriate, Phase I/II trials may be reviewed in conjunction with a disease treatment specific committee.

- Hematological Malignancies/Stem Cell Patient Care and Protocol Review Committee: 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. When necessary, the Committee also reviews audits of first patient entry on high-risk protocols involving ex vivo stem cell processing, gene therapy, and unrelated allogeneic stem cell donations. As appropriate Phase I trials maybe reviewed in conjunction with the Phase I Committee.

- Myeloma and Lymphoma Patient Care and Protocol Review Committee: This Committee reviews all patients active on myeloma/lymphoma protocols and evaluates laboratory and clinical data regarding toxicity, response, and drug tolerance. When necessary, the Committee also reviews audits of first patient entry on high-risk protocols involving ex vivo stem cell processing, gene therapy, and unrelated allogeneic stem cell donations. As appropriate Phase I trials maybe reviewed in conjunction with the Phase I Committee.

- Gene Therapy Patients are presented at either an ad hoc special committee(s), the Stem Cell or the Phase I meetings as approved by the DSTC and deemed appropriate for the protocol.

- Population Science and Bio-behavioral Research Review Committee: This group consists of members of the Population Science Research Program and Cancer Prevention and Control group with expertise in population and prevention methodologies, bioethics, clinical, behavioral and preventive medicine, biostatistics, community medicine methodologies, psychometrics and epidemiology. The committee is under the authority of the Medical Director for Clinical Trials. A pool of additional investigators are included in the review and monitoring of specific protocols as needed to provide specific content expertise and oversight of protocols for which standing committee members have a conflict of interest.

  Members of this committee may also provide pre-review of behavioral clinical trial protocols and determine the degree of risk. Based on risk, this committee makes a plan for oversight of the protocol for safety, adverse events reporting, data accuracy and protocol compliance, and stopping or suspension rules, as appropriate to the specific project. Because of the great heterogeneity in the degree of risk in behavioral research protocols, these plans vary with the specifics of the research project. Low risk protocols may be reviewed by the committee annually, whereas projects which contain a higher degree of risk may be reviewed more

frequently. Monitoring may involve electronic reporting and communication as well as individual meetings. The plan for review is agreed upon at the time of protocol approval by the PRMC.

Essential Elements of Data and Safety Monitoring Plan (DSMP)

The institutional Cancer Center Data and Safety Monitoring Plan (DSMP) is designed to provide the essential elements of data safety and toxicity reporting for all institutional investigator-initiated clinical trials. Each protocol will have a statement regarding compliance with the DSMP. If needed, there will be an additional statement regarding the particular unique features of data and safety monitoring required for a given protocol based on the medical or health-related context of the trial, its degree of risk, the size of the trial, whether it is multi-center, and whether review after first patient accrual is required based on the novelty of therapeutic intervention or the degree of risk. In general, protocol-specific DSMPs provide succinct addendums to the institutional DSMP.

Monitoring Progress of Clinical Trials and Patient Safety: Research nurse/coordinators monitor all patients on Phase I through Phase III clinical trials. Study or research coordinators assess patients on population science or behavioral clinical trials. Research nurse/coordinators evaluate patients as appropriate for the particular clinical trial and report findings of all active patients at the appropriate patient care Protocol Review Committee as noted above. The intensity of monitoring for toxicity is adjusted to the risk presented by the therapeutic intervention; greater risk in Phase I (dose-finding) and cell and gene therapy (dose-intense) trials than Phase II trials and NCTN Phase III trials. At Patient Protocol Review Committee meetings printed spreadsheets describing the patients' demographics, laboratory findings, and toxicity are reviewed by the research nurse/coordinators, attending physicians, and PIs.

D. EMERGENCY (COMPASSIONATE) USE OF INVESTIGATIONAL DRUGS

The use of certain treatment protocols, not formally reviewed or approved by the PRMC, may be made available to investigators through an ***Emergency Use*** process. This process provides the investigators with a protocol using an IND drug not available through normal systems of commercial availability or the MBRCC clinical trials offerings. It is recognized that extenuating circumstances make this mechanism the most expedient manner in which a patient may receive treatment for an obscure disease or with a pharmaceutical protocol not readily available. Emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a research activity. However, MBRCC investigators are strongly encouraged to pursue the development of new agents through the systems established in the clinical trials program. The following policies and procedures are applicable when an investigator requests approval of a protocol for emergency use:

- Emergency use protocols should not supersede existing MBRCC-approved protocols designed for similar clinical situations.
- Emergency use protocols are wholly appropriate for activation on a **one-time** basis for situations where there are no existing MBRCC protocols and/or the availability of select pharmaceutical agent(s) are non-existent without protocol engagement.
- The CTRU Regulatory Office must be notified when requesting approval of an emergency use protocol. This office will assist the investigator in his/her effort in obtaining necessary regulatory approvals.
- All clinical care and data management requirements are the responsibility of the investigator.
- CTRU staff will not participate in the management of these patients.

Emergency use protocols are limited to a **one-time** specific clinical (patient) event. The intent to enroll additional patients on such a protocol will mandate the submission as a new protocol and review and approval by the PRMC and IRB before such a registration accrual can be made.

III. PROTOCOL DEVELOPMENT

A. PROTOCOL DEVELOPMENT PROCESS

The following procedure is adhered to for the initial processing of CDAs, LOIs and protocols:

Confidentiality Disclosure Agreements

Investigators and/or Study Coordinators bring Confidentiality Disclosure Agreements (CDAs) from pharmaceutical sponsors to the Director CTRU for institutional routing and signature. Technology Transfer, from the WVU Office of Sponsored Programs, signs and submits the CDA to the pharmaceutical sponsor. Original copy of the CDA is filed in Technology Transfer office. CTRU then receives a copy of the protocol to proceed with feasibility and assessment for participation by the respective Clinical Trials Disease Team(s).

Concept / Letter of Intent (LOI)

Before development of a formal protocol, investigators are encouraged to bring to the Clinical Trials Disease Teams and/or to the Protocol Review and Monitoring Committee the objectives of the proposed trial in the form of a Concept / Letter of Intent (LOI) for review. The proposed trial will be discussed, with the investigator present, from the following points of view.

- Scientific merit.
- Statistical methodology.
- Relationship to ongoing protocols.
- Accrual goals.
- Funding potential.

It is appropriate and desirable that the protocol LOI for clinical research proposals that are being sent to the NIH/NCI for future consideration be submitted beforehand to the Protocol Review and Monitoring Committee and the Clinical Trials Disease Team. This will provide initial scientific input, assure proper priority for the project, and facilitate consistency and completeness in keeping with Mary Babb Randolph Cancer Center protocol requirements.

Investigator Initiated Protocols

A protocol template is required for these projects in order to submit to the PRMC and WVU IRB. The elements of the protocol template are detailed in Appendix 5 and can be found in the CTRU website: http://www.hsc.wvu.edu/ctru/investigator-services/

CTRU Administrative Office can assist investigators with organizing LOIs into a standard protocol template.

- All investigator-initiated LOIs and protocols must be electronically submitted to the CTRU Director and Manager for review of completeness.
- A protocol budget is prepared by the investigator in conjunction with CTRU Director.
- Any further changes are discussed with the investigator.
- The protocol is then reviewed by the Research Nurse/Coordinator and Regulatory Management.
- Final protocol revision is reviewed by the respective Clinical Trials Disease Team and signed off by the appropriate team leader using the PRMC Submission Form. (Appendix 3)
- The protocol and completed PRMC Submission Form is submitted to the CTRU Administration for submission to the PRMC for review.

Investigator initiated protocols that will receive drug from a Sponsor may need to file an Investigational New Drug (IND) application with the FDA or cross-file on a Sponsor's IND for a drug. See FDA IND Application for more information.

If the IIT involves a device, there is the possibility you may need to file an Investigational Device Exemption (IDE) application with the FDA or cross-file on a Sponsor's IDE for a device. See FDA IDE Application for more information.

B. PROTOCOLS INVOLVING CHART REVIEW ONLY

Investigators (or their designees) are required to submit chart review studies to the PRMC. These types of studies will be reviewed by the Committee Chair (or his designee) and included in the PRMC minutes. Submission of chart review studies to the PRMC will not delay IRB submission or IRB approval. IRB processing can occur simultaneously. In some cases, the CTRU Regulatory Office will prepare the IRB submission packet.

The following instructions apply for submission to the PRMC:

- Submit a PRMC Non-Treatment Submission Form (Appendix 3) along with the research plan to the PRMC Coordinator. This will add the chart review to the next PRMC agenda.
- In the research plan include:
    - A summary of the population to be studied.
    - A rationale of the study.
    - A description of the information that is being collected and why.
    - A statement that patients will not be contacted.
    - A description of how the information will be kept confidential.
    - An explanation of data analysis.

- References.

- At the end of the study or the end of each calendar year, report the number of charts reviewed to the PRMC Coordinator for MBRCC accrual reporting.

C. POPULATION SCIENCE AND BIO-BEHAVIORAL PROTOCOLS

Population science and bio-behavioral research protocols often are integrated into a research grant proposal that is submitted for peer-review and funding. Investigators (or their designees) are encouraged to submit proposals to the Population Science and Bio-Behavioral Review Sub-committee one month prior to submission if feedback is desired and following award for required review/monitoring. All protocols go to the PRMC first, the PRMC then distributes protocols to the Population Science and Bio-Behavioral Sub Committee as appropriate. In this manner protocol review and record keeping will be greatly facilitated.

Submit a PRMC Non-Treatment Submission Form (Appendix 3) and protocol to the PRMC Coordinator.

A protocol template is required for these projects in order to submit to the PRMC and WVU IRB. The elements of the protocol template are briefly listed below and details are provided in Appendix 5. It is noted that for the majority of population science or bio-behavioral research protocols, treatment, study parameters and drug sections are not necessary.

At the end of the study or the end of each calendar year subject accruals must be submitted to the PRMC Coordinator for MBRCC accrual reporting.

IV. PROTOCOL ACTIVATION PROCESS

A. INSTITUTIONAL APPROVAL PROCESS

The WVU IRB requires that all cancer-related clinical research involving human subjects be reviewed and approved for scientific merit by the Mary Babb Randolph Cancer Center PRMC before consideration/approval by the IRB. See accompanying letter from Daniel Vasgird, Director of the Office of Research Integrity and Compliance in Appendix 4.

The IRB also requires departmental/section sign off. The Physician-in-Chief of Oncology provides this departmental approval for all Mary Babb Randolph Cancer Center protocols. Protocols, defined by their patient population or treatment modality, are sent for Departmental approval by the respective department or section, i.e., Surgery, Pediatrics, Urology or Gynecology.

The CTRU Regulatory Office staff assists investigators with protocol submission to the IRB in a format adhering to all local jurisdiction requirements. This includes submission of the full protocol and consent. This effort is performed in concert with the PI. The IRB determines review priority for their committee, but is sensitive to protocols defined as high priority for the Mary Babb Randolph Cancer Center as defined by the PRMC. The CTRU Regulatory Office staff assists investigators with implementation of changes or modifications to consent forms at the direction of the IRB; IRB approval is provided on the consent used for all active MBRCC clinical trials.

Protocol Review and Activation Process

The table below outlines the protocol review procedural process and identifies responsible staff.

ACTIVATION ACTION ITEM	RESPONSIBILITY
1. Preparation for PRMC Review	
a. Present protocol at respective Disease Team meeting.	Principal Investigator
b. Submit Disease Team review sheet for PRMC submission to PRMC Coordinator	Principal Investigator
c. Assign research nurse, protocol coordinator and data manager	Manager, Oncology Clinical Services
d. Submit in OnCore®	Study Coordinator
e. Place on Agenda for PRMC	PRMC Coordinator
f. Assign protocol number (if applicable)	PRMC Coordinator
g. Collate and deliver protocols for meeting	PRMC Coordinator
2. MBRCC Protocol Review	
a. Scientific Review b. Scientific merit c. Prioritization for patient resources	PRMC Committee
d. Biostatistics Review i. Measurement of effect ii. Study parameters iii. Statistical considerations	Biostatistics Core Facility via PRMC
e. Trial Administration i. Protocol eligibility checklist ii. Measurement of effect iii. Study parameters iv. Records to be kept v. Complete consent form adherence checklist	CTRU Staff

vi. Develop budget vii. Protocol log file viii. Update priority listing	
f. Pharmacy review i. Drug formulation/procurement ii. Medication checklist sign-off	Investigational-Pharmacy Representative
g. Notify PI of PRMC decision	Chair and PRMC Coordinator
h. Prepare minutes	Chair and PRMC Coordinator
i. Distribute minutes for review to PRMC and PI, memo to PI, memo to IRB	PRMC Coordinator
j. Update electronic database	OnCore® Administrator
3. External Committee Reviews	
a. Prior or concurrent to PRMC review (Biosafety; Radiation Safety; Infectious Diseases)	PI, Study Coordinator
4. New IRB Application	
a. Abstract protocol and consent form for IRB application	Study Coordinator, Data Manager, Regulatory Office
b. Obtain departmental electronic signatures	CTRU Regulatory Office
c. Submit to appropriate IRB along with copy of PRMC approval and CTRU Regulatory Office approval.	CTRU Regulatory Office
d. Make changes to consent form per IRB recommendations	PI, CTRU Regulatory Office
e. Distribute IRB approvals as needed	CTRU Regulatory Office, Network Coordinator
5. Continuing Review for IRB (annually)	CTRU Regulatory Office
a. The IRB system automatically notifies study team of protocols due for continuing review at 60 and 30 days in advance.	CTRU Regulatory Office
b. Review list of protocols	CTRU Staff, Regulatory Office
c. Remind investigator and research nurse/coordinator that continuing review is due.	CTRU Regulatory Office
d. Request data to compile report from research nurse/coordinator and/or data manager	CTRU Regulatory Office
e. Prepare continuing review	CTRU Regulatory Office
f. Send to DSTC	CTRU Regulatory Office
g. Submit continuing review to IRB	CTRU Regulatory Office

Investigator-initiated, pharmaceutical, and NCTN sponsored protocols will be activated when all of the following procedures have occurred as outlined below by clinical trial sponsorship:

	Investigator Initiated (IIT)	Industry Sponsored (IND)	National Clinical Trials Network (NCTN)
Regulatory Approvals			
☐ PRMC Approval	X	X	X (Admin Review)
☐ IRB Approval	WVU IRB	Chesapeake IRB or WVU IRB	NCI CIRB or WVU IRB
☐ Associated committees (biosafety, radiation, population sciences, etc.)	X	X	X
☐ CTSU website site registered and compliance	n/a	n/a	X
☐ FDA Approval (if applicable with IND)	X	n/a	n/a
☐ Protocol registered on clinicaltrials.gov if applicable	X	n/a	n/a
Financial Approvals			
☐ Approved Budget	X*	X	n/a
☐ Medicare Coverage Analysis		X	X
☐ Clinical Trials Agreement/Contract signed off	X	X	n/a
Clinical Approvals			
☐ Study team members (Research Nurse/Coordinator and Data Manager) have been assigned.	X	X	X
☐ Study specific order sets have been developed	X	X	X
☐ Lab and other study required supplies and investigational drugs have been received	X	X	X
☐ Case report forms (CRFs) have been reviewed (or databased released) and the CTRU staff have been trained.	X	X	X
☐ Protocol specific training is provided to study team and documented and filed with protocol essential documents.	X	X	X
☐ If required, radiation credentialing has been completed	n/a	n/a	X
☐ All regulatory documents have been filed with the sponsor	n/a	X	n/a
☐ Activation at collaborating institutions - The CTRU administrative staff assists the PI in	X	n/a	X

compliance and activation at selected collaborating institutions.			
☐ The activation checklist has been completed.	X	X	X
☐ An activation date is recorded in the MBRCC electronic OnCore® database.	X	X	X

* A budget has been approved either through outside support and completion of a Clinical Trials agreement or through internal Cancer Center funds approved by the Mary Babb Randolph Cancer Center Senior Leadership Committee.

Budgets and Contracts

Due to the complexity and financial ramifications of an improperly funded trial, we ask that you not negotiate with any sponsor directly. All trials, regardless of funding mechanism, will require an internal budget developed for review and fiscal feasibility. The Director of the Cancer Center will make the final determination regarding feasibility of opening a trial that has financial shortages.

Common areas to review in budgeting:

Protocol related activities

- Includes PRMC and IRB submissions, as well as
- Collection of essential documents
- Continuing reviews and amendment processing
- Outside Safety Reports (OSR), Serious Adverse Events (SAE) processing
- Monitoring time and sponsor related reporting

Patient related activities

- Research related testing
- Use of Bio Specimen Processing Core for specimen collection and shipping
- Use of outside departments, such as Pathology, Radiology, Cardiology, etc.
- Reimbursement for drug administration, patient travel, time, etc.

Salary support

- Principal Investigator (includes time for oversight of the trial)
- Nursing oversight
- Data management

IRB fees

- Fee structure for initial review, continuing review and amendments determined by IRB of record

Fiscal

- 26% overhead for industry
- Budget and contract preparation, negotiation and management
- External monitoring/audits for multi-site trials
- Indemnification insurance for multi-site trials

Investigator Initiated Trials Budgeting

If you will be requesting industry support for an IIT or a grant, it is imperative to notify the budget staff in the CTRU at the time of LOI so they can aid in determining an appropriate funding request. The CTRU will aid in collecting discounted rates for research related testing, correlative testing through the BPC and compiling standard protocol related fees, salary fees, etc.

Once the final protocol has been developed, the budget staff will finalize your per patient dollar amount and aid you in requesting support from the MBRCC leadership if the trial is not fully funded.

Industry Sponsored Budgeting

The CTRU budget staff will aid in budget negotiations with all industry sponsors. The budgetary process begins once the staff is notified a trial has received PRMC approval. The budget analyst will meet with either the PI or the Coordinator to review the protocol details for research related activity. Once this is complete, the staff will compile and appropriate per patient budget and negotiate on your behalf with the sponsor. After a budget agreement has been made, the budget analyst will review the details with the PI prior to finalizing the contract.

Contracting

Industry Supported or Sponsored Trial Contracting:

After the budget agreement has been made the budget staff forwards a copy of the budget to the WVU Office of Sponsored Programs (OSP). OSP legal counsel negotiates the contract with the sponsor until the contract language is agreeable to both parties.

Investigator Initiated Trial Contracting:

One common area of difference in contract language review is in regards to intellectual property and/or publishing rights. Please notify the contracting coordinator if you have any specific interest in a trail IP or publications.

If you intend to subcontract with other sites, please identify this up front to allow subcontracts to be developed. Each participating institution will require a separate contract and will need to be written in accordance with our prime agreement.

Subcontracting from another institution:

If you choose to be a PI for a non-MBRCC investigator initiated trial, a subcontract is required with the lead institution with a budget and data agreement included.

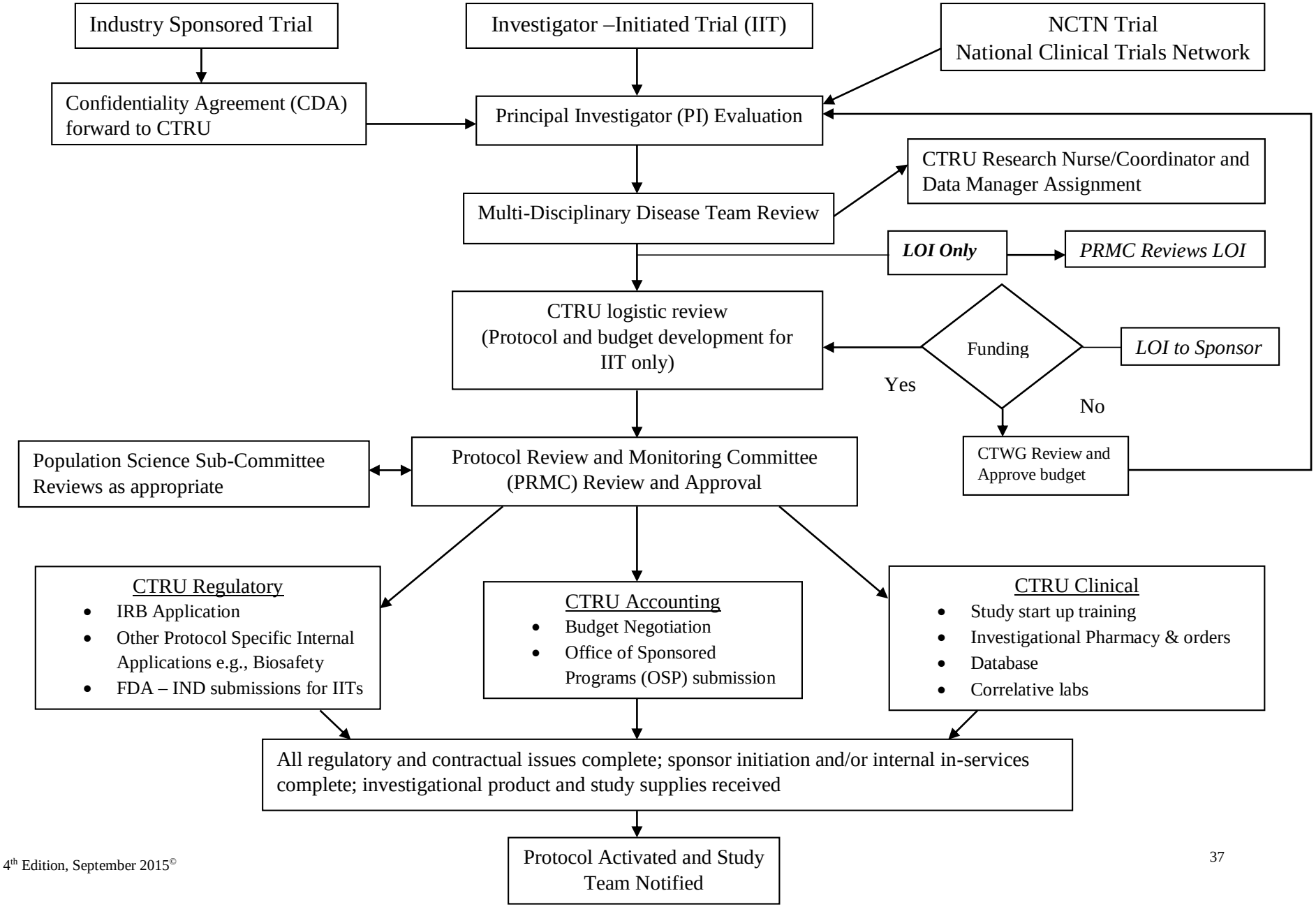
Communication and Notification

The Medical Director for Clinical Trials (for treatment and non-treatment clinical trials) or the Associate Director for Population Research (for population science and behavioral studies) sends an official notice to all MBRCC study team members with protocol activation. Please refer to the OnCore® database for protocol and priority details.

All MBRCC protocol documents will be attached in the OnCore® database, available to all Cancer Center members with, access privileges, in its full form. This electronic system maintains a listing of all MBRCC clinical trial protocols by disease, by phase and protocol number. The full text of the protocol is listed including current amendments so that all investigators have access to correct and complete trial availability. Trial consents are only available to the PIs, sub-investigators, and key personnel and attached in OnCore.

WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

MBRCC: New Protocol Pathway



B. COLLABORATIVE SITE ACTIVATION

The Mary Babb Randolph Cancer Center Instructions for Collaborating Institutions outlines the specific regulatory documents required for each site. See Appendix 2.

Once the collaborating institution's IRB approval, consent approval, and regulatory data have been reviewed and accepted, the collaborating institution's PI and/or designee is notified via email the protocol is ready to open for accrual at his/her site. At that time, a site initiation telephone call/ webinar is conducted to include the MBRCC PI, Research Nurse/Coordinator, Data Specialist and Network Coordinator/Quality Assurance (QA) Specialist together with the research staff from the collaborating site(s). The site will receive instructions as to data expectations and study conduct; with contact information of the MBRCC research team provided. The MBRCC Research Network Coordinator acts as a liaison to facilitate regulatory and protocol compliance throughout the conduct of the study.

V. INVESTIGATOR RESPONSIBILITY

Investigator responsibilities are outlined herein and further described in Appendix 6.

Physician investigators require the following training, qualifications and commitments:

- Human Subject Protection Training (CITI- Biomedical Research Investigators)
- Conflict of Interest Training (CITI- Conflicts of Interest)
- Professional appointment
- Current CV (signed and dated annually)
- Copy of medical license
- NCTNs registration
- NCI/CTSU registration (including NCI Support Information form, Financial Disclosure form and 1572)
- 1572 Statement of Investigator form – By signing the 1572 the investigator commits to the following:
    - Agreement to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects. Agreement to personally conduct or supervise the described investigation(s).
    - Agreement to inform any patients or any persons used as controls that the drugs are being used for investigational purposes and they will ensure that the

requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

- Agreement to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
- He/She has read and understands the information in the investigator's brochure (IB), including the potential risks and side effects of the drug.
- Agreement to ensure that all associates, colleagues, and employees assisting in the conduct of the study (ies) are informed about their obligations in meeting the above commitments.
- Agreement to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- Ensures that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. He/She also agrees to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, he/she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- Agreement to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

At the time of IRB submission for a new protocol, investigators are asked to certify the following:

- They will not initiate this study until they have received written approval from the IRB.
- They will promptly report to the IRB any unanticipated problems and adverse events, as well as any findings during the course of the study that may affect the risks and benefits to the subjects.
- They will obtain prior written approval for modifications to this protocol, including but not limited to, changes in procedures.
- They are currently certified under the Research Compliance Education Program administered by WVU or will achieve certification before subjects are enrolled in this protocol.
- They accept responsibility for assuring adherence to applicable federal and state research regulations and hospital policies relative to the protection of the rights and welfare of the subjects enrolled in this study.

- They are in full compliance with the university's/institution's policies on Conflict of Interest.
- They understand that the IRB office operates under a Federal Wide Assurance (FWA) from the Department of Health and Human Services.
- They understand that this study is subject to continuing review and approval by the WVU IRB.
- Hold periodic meetings with study team to discuss trial progress, protocol updates, adverse events, etc. Meeting minutes shall be taken and filed with protocol essential documents.
- Attend Cancer Center clinical trial continuing education seminars. Attendance is mandatory and will be documented and filed in CTRU Administrative Office.

VI. REQUIRED CERTIFICATION AND TRAINING

The Mary Babb Randolph Cancer Center adheres to local presiding IRB guidelines for Human Subjects Research Protection. The WVU IRB requires certification of the PI and anyone who obtains written consent for the protocol. This requirement applies to all Mary Babb Randolph Cancer Center CTRU staff.

Once certified, all investigators must maintain valid certification by participating in ongoing continuing education programs. The Collaborative IRB Training Initiative (CITI) web-based program is available as an option to meet both initial core certification and continuing education requirements.

A. NATIONAL CANCER INSTITUTE (NCI) REGISTRATION

Food and Drug Administration (FDA) regulations and NCI policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the completion and submission of each of the following three forms accompanied by a current CV.

- Statement of Investigator Form (FDA Form 1572)
- Supplemental Investigator Data Form (IDF)
- Financial Disclosure Form (FDF)
- Current Curriculum Vitae (CV)

More information is available at
http://ctep.cancer.gov/investigatorResources/investigator_registration_packet.htm

Cancer Center members can choose to have the CTRU assist with NCI registration. If you choose to use the CTRU, our staff will fill out the paperwork and submit to the NCI for you. We will need your original signature on the application.

Following registration you will receive a renewal application annually. If you are a Cancer Center member and inadvertently receive the renewal directly, please contact the CTRU office at 304-293-7374.

B. HUMAN SUBJECT RESEARCH CERTIFICATION FOR INVESTIGATORS

The Institutional Review Boards (IRBs) at West Virginia University have approved the use of the CITI training program for all individuals involved in human subject research. This course must be completed by all investigators and research staff. There are two separate modules, one for biomedical research and one for social and behavioral research investigators, IRB members must take both, while research investigators may choose the applicable specialty area. The WVU IRB requires that CITI training be completed every three years using the CITI Refresher Courses.

You should go to https://www.citiprogram.org. Once there, click on the link *Register Here*. Under Institution selection, scroll to West Virginia University. Once there, create a username and password (Use of Outlook user name will facilitate our keeping track of you). Select the CITI recommended learner group, biomedical research, social and behavioral research, or IRB members. Note you do not have to complete the training in one session.

C. GOOD CLINICAL PRACTICE (GCP) TRAINING

Good Clinical Practice (GCP) is the FDA standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials. The Mary Babb Randolph Cancer Center adheres to these standards and **strongly encourages** all investigators, and research staff to be familiar with GCP standards. To help ensure all those involved in clinical research adhere to GCP standards, the CITI website offers GCP training. Cancer Center faculty and staff are **strongly** urged to complete this training.

Once you are registered in CITI program, click on "add a course" and go to question 6 and chose GCP training. Now the course has been added to your list of courses to complete.

FDA GCP Guidance for Industry can be found at the following site:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf

D. CONFLICT OF INTEREST (COI) TRAINING

The new NIH guidelines require all investigators receive COI training prior to submitting their COI disclosure forms. This training must be done every four years. As per the new federal regulations, WVU Research Administration cannot accept grant, IRB, or IACUC applications from any investigator, including key personnel, until all have complete their COI training.

The guidelines define an investigator as any individual, regardless of title, role or position who is responsible for the design, conduct, or reporting of research. Individuals with such research responsibilities may be, but are not limited to, senior/key personnel, sub/co-investigators or sub-recipient investigator, medical investigator, collaborator, consultant, student, trainee, or research coordinator.

Training can be completed through the COI course offered on CITI.

To access the required training, go to the CITI Website at https://www.citiprogram.org/.

1. Choose "Add a course or update your learner groups for West Virginia University"
2. Answer Yes to Question 2, "Would you like to take the Conflicts of Interest course?"
3. Click on "Continue" at the bottom and complete the required modules.

E. CANCER CLINICAL TRIALS 101

The Clinical Trials Working Group (CTWG), [under the auspices of the Clinical Trials Monitoring System (CTMS) and specifically the Protocol Review and Monitoring Committee (PRMC)] organizes a triennial conference for continuing education on general topics of importance and conduct of cancer clinical trials to investigators and research personnel.

In the evolving and highly interactive regulatory and monitoring environment now required for the pursuit of human subject investigations and clinical trials, a continuing education program is needed. This program provides contemporary information about regulatory guidance, research compliance, and ethics of clinical trials, human subject protection, and general training about clinical trials conduct among other topics of importance as they arise.

This venue will also provide an opportunity for review and self-reflection of our clinical trials research program(s), policies and procedures that are subjected to the myriad of reviews, audits and annual reporting that the Clinical Trials Research Unit (CTRU) participates in annually.

The *Cancer Clinical Trials 101* course is held triennially at the Health Sciences Center. An agenda is distributed prior to the conference; minutes are kept and distributed; attendance is recorded and mandatory (2 out of 3 conferences per year) for all clinical investigators and research personnel participating in our Cancer Center clinical trials program. The WVU Office of Research and Integrity Compliance, acknowledges this continuing education effort. (See accompanying memo from Dr. Daniel Vasgird, Director of the Office of Research Integrity and

Compliance in Appendix 4. The conference is fully aligned with FDA guidance for clinical trials continuing education programs.

VII. SUBJECT MANAGEMENT AND DATA ACQUISITION

The Clinical Trials Research Unit is responsible for the registration of patients and data acquisition for all cancer investigator-initiated, pharmaceutical-sponsored, or NCTN, protocols. All required patient information is entered into the electronic database for all MBRCC protocols according to the schedule outlined within each protocol. The OnCore® interactive database allows remote entry from satellite or affiliate institutions, subject to review by the CTRU. For NCTN or pharmaceutical protocols, the CTRU is responsible for the submission of required data forms to the designated data center. For these patients, the CTRU maintains data on patient registration, adverse events and survival only. Research nurses, protocol coordinators and data managers serve as study coordinators and may perform all the tasks described below.

A. ELIGIBILITY

- Prior to registration, the Research Nurse/Coordinator completes the eligibility from the protocol and along with supporting source documents, and signed consent, presents it to the QA Specialist for verification and sign-off. This applies to interventional trials only, e.g., treatment, supportive care, prevention intervention trials.

- The enrolling physician must approve eligibility and sign and date the eligibility checklist. PI's co-sign at the earliest possible date, if different from enrolling physician.

- If the Research Nurse/Coordinator has concerns about eligibility, consent, etc., these concerns are directed to and adjudicated by Medical Director for Clinical Trials, or Chair PRMC, or Chair DSTC, or Cancer Center Medical Director or Cancer Center Director.

- After eligibility and consent is approved, the Research Nurse/Coordinator proceeds with placing the subject on-study per sponsor guidelines and completes the registration process.

B. PROTOCOL EXCEPTIONS

Eligibility, Study Parameters or Treatment

Protocol exceptions are defined as circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient/subject (example: patient/subject is allergic to one of the medications provided as supportive care). Usually it is a violation that is anticipated and happens with prior agreement from the sponsor.

All protocol exceptions are reviewed by the DSTC at the meeting following authorization. The DSTC can determine at any time that a protocol amendment is required. The Medical Director for Clinical Trials will be made aware of all protocol exceptions prior to submission to the IRB.

Guidelines for Protocol Exceptions for Investigator Initiated Trials

By CTEP decree, there are **no exceptions** for CTEP sponsored trials. For non-CTEP sponsored investigator-initiated protocols, exceptions for eligibility, study parameters or treatment may be requested. Objective numerical data for protocol eligibility (e.g., Hgb ≥ 9.5 g/dl; creatinine ≤ 2.0 mg/dl; LVEF ≥ 40%) are not subject to exception. In rare instances a protocol may allow variance in numerical eligibility criteria.

The exception process is as follows:

- The research nurse/coordinator will present the exception request to the PI. If the PI agrees to the exception, he/she must provide approval in writing.
- If it is the PI is requesting the exception, he/she must have two independent (not associated with study) physicians review and advise the DSTC (on behalf of the PRMC) on the appropriateness of the exception.
- If the two independent reviewers agree, the exception will be presented to the Medical Director for Clinical Trials for written authorization. The protocol exception will be accepted. If the independent reviewers disagree or the Medical Director for Clinical Trials will not authorize, then the exception is denied and there is no further recourse available.
- The research nurse/coordinator will provide a copy of the reviews and authorization to the CTRU Regulatory Office who will then submit the exception to the WVU Institutional Review Board for approval **prior to implementation**.
- Second same exceptions **are not** allowed. In such cases, an amendment to the protocol should be developed.
- There will be no retroactive exceptions.

Guidelines for Protocol Exceptions for Pharmaceutical and NCTN Trials

Any protocol exception to be considered must follow the procedures outlined below:

- The investigator must confirm in writing with the sponsor (Medical Monitor or Protocol Chair) that authorization for the exception is granted.
- The research nurse/coordinator will provide a copy of the sponsor's authorization to the CTRU Regulatory Office who will then submit the exception to the WVU Institutional Review Board for approval **prior to implementation**.

C. INFORMED CONSENT

Informed Consent should be provided to the patient in both a written and verbal manner with an opportunity for questions and answers. The consent form must be signed by the patient in the presence of the PI or Co-I or appropriately trained personnel. The PI or Co-I signature must be contemporaneous and present on the consent form prior to the patient initiating investigational treatment. For non-therapeutic trials or population-based, behavioral or prevention studies the protocol coordinator or research nurse signs the informed consent and enrolling physician may sign at a later time. All patients will receive a copy of their signed informed consent. If the patient is not able to provide consent for the clinical trial, the only person that may give the patient's consent to participate is the patient's legal guardian. Verification of guardianship is required. If the patient is unable to read or a legally authorized representative is unable to read, an impartial witness should be present during the entire informed consent discussion. This witness, in addition to the patient or their legally authorized representative, and the PI or Co-PI, should sign the informed consent. Consenting vulnerable populations are guided by local IRB mandates. Informed Consent must be obtained prior to any procedures to be performed that are directly related to research. The Informed Consent process must be adequately documented in the original source document and must include:

- Date of the consent.
- Name of the protocol.
- Statement that identifies the site personnel who obtained the informed consent.
- Statement that the patient was given the opportunity to review and ask questions or voice concerns.
- Statement that a signed copy of the consent form was presented to the patient.

D. HIPPA AUTHORIZATION

Health Insurance Portability and Accountability Act of 1996

The HIPAA authorization information is incorporated within the patient consent form and will not be a separate document. The research team is responsible for identifying the HIPAA Authorization to the patient at time of the review of consent and obtaining signature.

E. REGISTRATION PROCESS

The enrolling physician must sign and date the eligibility checklist acknowledging they agree that the subject is eligible. The PI co-signs (if necessary), at the earliest possible date of consent. The original signed informed consent must be provided for review and verification. After eligibility is reviewed and documented by the QA Specialist, the research nurse/coordinator will

complete the registration process with the sponsor and update the clinical trials database, OnCore® with assigned protocol treatment per OnCore® Guidance Document.

Certain protocols allow for treatment prior to registration over weekends, holidays or emergency conditions.

F. ON STUDY DATA

The research nurse/coordinator abstracts the information from the medical record onto the Patient History File, the Case Report or On-study Form; this data is entered into the OnCore® database.

G. RESPONSE DATA (INVESTIGATOR INITIATED TRIALS)

With the help of the Imaging Research Specialist, it is the Radiologist's responsibility to follow and document measurements of target/non target lesions consistent with response criteria that is defined in the protocol (RECIST 1.1, and Lymphoma Criteria). The PI, with the help of the imaging specialist and radiologist, is responsible for determining response of the designated lesions utilizing the protocol defined response criteria based off of the measurements from the radiologist. The PI will sign the appropriate data form and give to the study coordinator for entry into the database.

If by the response criteria defined in the protocol the investigator believes a response has occurred, the patient will be reevaluated at a second interval evaluation as defined in the protocol. If at the second interval evaluation, the investigator still believes the patient has achieved a response, the research nurse/coordinator will bring the supporting evidence to the DSTC for review and independent confirmation. The response is considered unconfirmed until the DSTC verifies it. No external reporting or recording of responses can be released until the DSTC confirms the response.

RECIST 1.1 http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

Lymphoma Criteria:

http://jco.ascopubs.org/content/25/5/579.full.pdf+html
http://jco.ascopubs.org/content/25/5/571.full.pdf+html

H. SERIOUS ADVERSE EVENTS

Serious adverse event: An adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent of the outcomes listed above.

SAEs are documented and reported as defined per the protocol and the MBRCC DSMP. SAEs that require expedited reporting will be entered into the OnCore® database and reviewed by DSTC and WVU IRB (or respective IRB of record) as defined in the respective policies.

Tabulation of Serious Adverse Events Reporting Process

SAE REPORTING ACTION ITEMS	RESPONSIBILITY
Toxicities (expected/unexpected) reported as soon as identified per protocol guidelines. Anyone can/should report possible toxicities to study coordinator.	Physician, Nurse, Study Coordinator
Provide SAE report to the appropriate agency (NCI/CTEP, FDA, OBA, NIH, NCTN, pharmaceutical company liaison) using the NCI and/or protocol guidelines.	Physician and Study Coordinator
Enter SAEs that require expedited reporting per the protocol into the OnCore® database.	Study Coordinator/Data Manager
SAE reported to Medical Director of CTRU, DSTC and IRB per applicable policies.	DSTC Coordinator/QA Specialist/Regulatory

I. OFF STUDY / COMPLETION OF TREATMENT / FOLLOW UP

- Off-treatment indicates that a patient is no longer treated but remains actively followed per study guidelines.
- On-follow-up indicates data to be recorded for a patient who is on study and has reached an interim assessment point. These events are logged into the database as per study requirements such as disease-free survival (DFS) and overall survival (OS).
- Off-study indicates that the patient has completed study requirements, has met an off-study endpoint such as disease progression, post-treatment follow-up duration endpoint or has died.

- After determination by the physician of a recurrence or second malignancy, the research nurse/coordinator records the information onto the appropriate data form. As required, secondary malignancies are reportable to the NCI, the local IRB and/or other sponsors.

DATA ACQUISITION PROCEDURES

ACTION	RESPONSIBILITY
1. Informed Consent	
a. Obtain informed consent	Physician/Study Coordinator
b. Place original ICF/HIPAA in the patient's protocol chart and a copy in the patient's medical record.	Study Coordinator
c. Hand deliver a copy of the ICF/HIPAA to patient	Study Coordinator
2. Eligibility	
a. Complete eligibility checklist	Study Coordinator
b. Check, sign and date eligibility checklist	Physician
c. Submit eligibility checklist to QA for secondary review	Quality Assurance
d. Place signed eligibility list in protocol chart	Study Coordinator
3. Registration	
a. Register the patient with the CTRU, or the appropriate agency (NCTN statistical center or pharmaceutical Co., including randomization, if applicable)	Study Coordinator
b. Patient case number assigned at the time of registration	CTRU
c. Record consent, eligibility, on study and treatment assignment in OnCore.	Study Coordinator/Data Manager
d. Registration procedure must be completed before treatment begins	Physician and Study Coordinator
4. On Treatment	
a. Obtain patient history to include diagnosis, prior treatment, medical history, physical exam, medications, tumor assessment and labs	Physician / Clinic Nurse
b. Abstract patient history onto the patient history file and the case report or on-study form and into OnCore database.	Data Manager
c. Abstract prior treatment, con meds per protocol	Data Manager
d. Follow protocol treatment schedule for data submission guidelines	Data Manger
5. Toxicities/Serious Adverse Events	
a. Toxicities should be reported as soon as identified. Anyone can /should report possible toxicities to study coordinator per protocol and IRB requirements	Physician, Nurse, Study Coordinator
b. Complete report. Submit to PI for review and signature	Physician and Study

	Coordinator
c. Provide oral and/or written report to the appropriate agency (NCI/CTEP, FDA, OBA, NIH, NCTN, Pharmaceutical Co. liaison) using the NCI and/or protocol guidelines. File CTEP-AERS as required	Physician and Study Coordinator
d. Submit SAEs to DSTC	Administrative Director, DSTC
e. Enter toxicities in database	Data Manager
6. Response	
a. Measurement (solid tumors): complete tumor measurement worksheet and perform needed computations	Physician and Study Coordinator
b. Determination of response and sign-off of appropriate work-sheet	Physician
c. Record onto appropriate agency form or CTRU follow up form	Study Coordinator / Data Manager
d. Enter responses in database	Data Manager
7. Recurrence and Survival	
a. Determination of recurrence and survival status	Physician and Study Coordinator
b. Record onto appropriate Agency Form or the CTRU f/u form	Study Coordinator / Data Manager
c. If patient death occurs, record death information onto CTRU f/u form. Death information must be accompanied by source documentation.	Study Coordinator

VIII. PROTOCOL MONITORING

A. THE ROLE OF THE BIOSTATISTICS CORE FACILITY IN MONITORING

Data Monitoring

The Biostatistics Core Facility prepares summaries and monitoring reports on items such as the following: diagnosis, registration and randomization, baseline characteristics, treatment delivery, toxicity, endpoints, and follow-up. The facility will track the progress of studies, [i.e., adequate accruals and evaluation of study endpoints, providing feedback to the PIs, the CTRU and the PRMC].

Review of Protocol Accrual and Adherence to Statistical Considerations

Accrual and adverse events will be monitored for each protocol to facilitate protocol monitoring for early stopping and interim analyses. For protocols with interim analyses timed according to

number of endpoints or number of subjects completing the protocol, relevant summaries of these benchmarks will be provided as well. These reports enable timely reminders to the principal investigators of important statistical events for either early stopping or interim analyses. The Biostatistics Core Facility facilitates the activities of the PRMC by advising as to whether protocol-defined stopping rules for reasons of efficacy or futility have been reached. It can also provide input as requested by the PRMC, for example in calculating conditional power of ongoing studies based on projected final enrollment.

B. ROLE OF CTRU IN MONITORING

A formal review of accrual for all active protocols is conducted on an annual basis. The CTRU and/or CTWG brings to the attention of the Clinical Trials Disease Teams, the Early Phase I/II, or Hematological Malignancy/Stem Cell Committees, as well as the PRMC, issues relating to the progress of the study such as deficient accrual, unexpected toxicity and adverse events. Disease responses and adverse events are reviewed by the DSTC. Specific issues relating to protocol activity are reported by the Team Leader to the PRMC. Final authority to reconcile any concerns or to adjudicate decision of the multi-disciplinary teams, PRMC, or DSTC rests with the CTWG about protocol sustainability or closure.

Regulatory Office Guidelines for Continuing Review Process

On each annual anniversary of a trial's initiation a brief narrative summary compiled with the PI, which discusses any significant results, toxicities experienced, numbers of patients accrued, and plans for continuation of the trial is submitted to the IRB for review. For all investigator-initiated MBRCC trials, the continuing review is presented to the PRMC and to the appropriate Clinical Trials Disease Teams, the Early Phase I/II, or Hematological Malignancy/Stem Cell Committees. These groups report their review to the PRMC. Specific issues to be addressed by the PRMC include accrual, achievement of scientific endpoints and continued prioritization.

Monitoring of Early Phase Clinical Trials Requiring Special Data Monitoring Review

In addition to the routine monitoring of clinical trials outlined above, the CTRU maintains a procedure for independent monitoring of early phase investigator-initiated trials that are deemed high risk and consequently designated high priority for monitoring and review. Examples include gene therapy, cell expansion, novel agents not previously administered to patients and use of experimental devices. In these instances, the CTRU appoints a team of two research nurses and one physician not associated with the protocol to review the laboratory records, pharmacy records and treatment records to ensure that there is compliance with protocol guidelines, reporting procedures and toxicity reporting. This team reports to the PI, the appropriate Clinical Trials Disease Team, the Cell and Gene Therapy Subcommittee and the DSTC on its findings and verifies its review in the study chart and by co-signature of laboratory records, as indicated.

Role of the Clinical Trials Disease Teams

The Clinical Trials Disease Teams work in concert with the CTRU and Biostatistics Core Facility to provide input regarding continued level of clinician interest and support, issues with eligibility criteria affecting accrual, changes in clinical populations or concerns with trial logistics.

C. ROLE OF THE PRMC IN MONITORING

Toxicity and Response

The PRMC is charged with assigning a risk level to each trial as it pertains to patient safety. Clinical trials with an external DSMB or defined data and safety monitoring plan will be reviewed annually as outlined for low risk trials unless determined otherwise by the PRMC. The Early Phase I/II Patient Protocol Review 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). The Hematological Malignancy/Stem Cell Committee reviews all patients on active stem cell transplant and acute leukemia protocols and evaluates laboratory and clinical data regarding toxicity, response and drug tolerance. Patients on gene therapy will be monitored either by an ad hoc special committee or committee listed above, as deemed appropriate for the protocol. The Population Science and Bio-Behavioral Research Review Committee will monitor the number and demographics of research participants. The specific Clinical Disease Team Review Committee is required to report to the DSTC according to the scheduled as outlined in the MBRCC DSMP (Appendix 1). The schedule is based on the risk level assigned by the PRMC.

Protocol Closure

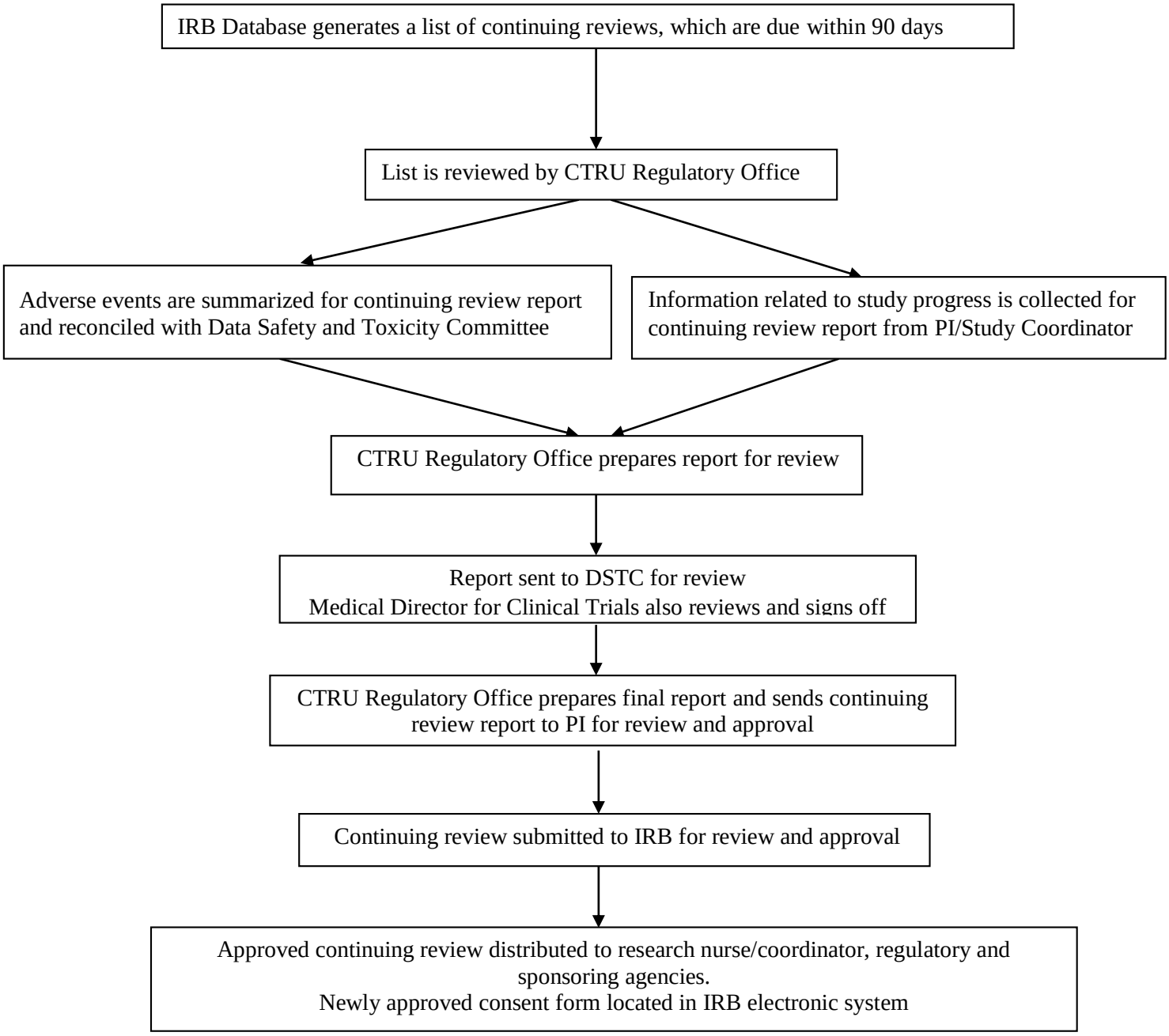
A recommendation for closure may be brought to the PRMC by the PI, the Clinical Trials Disease Management Team, DSTC and/or Clinical Trials Working Group. If the PRMC concurs with the recommendation, the decision to close a trial is communicated to the Medical Director for Clinical Trials. The Medical Director for Clinical Trials is authorized by the Cancer Center Director to close or suspend protocols for cause and will communicate that decision under his/her name to the members of the Cancer Center in writing.

The Biostatistics Core Facility facilitates the activities of the PRMC by monitoring accrual and other events relevant to planned interim analyses and built-in stopping rules, providing documentation and determining whether formal stopping rule boundaries have been reached.

After reviewing accrual, safety and toxicity data, and results of planned interim analyses of efficacy, the DSTC may recommend early stoppage of trials due to any number of reasons, including inadequate enrollment, safety/toxicity concerns, or stopping due to crossing of efficacy or futility boundaries. The DSTC, the PI, or the Sponsor, may make recommendation to the PRMC for protocol suspension. If an action is required before the PRMC can convene, a

protocol recommended for suspension can be directed to the Medical Director for Clinical Trials for action. A recommendation on whether to suspend the trial will then be considered at the next scheduled PRMC meeting. The decision to suspend or close a trial is communicated by the Medical Director for Clinical Trials to the PI, protocol sponsor and the IRB. Trials may be suspended by a sponsor or by the local IRB at their discretion. A protocol may always be closed at the direction of the local IRB or the sponsor. The PRMC complies and proceeds with routine closure procedure.

Protocol Monitoring and Oversight



IX. QUALITY ASSURANCE

A. INTERNAL AUDIT PROCESSES

Standard Investigator-Initiated Trials Audit Process

Audits will be conducted in the interest of improving quality control, protocol compliance, and data management procedures as described in the MBRCC Data Safety Monitoring Plan, DSMP. (Appendix 1) In general, all therapeutic investigator-initiated trials will have an audit performed on the first patient enrolled to the protocol. All trials determined to be high risk (as determined by the PRMC) will be audited on a routine basis. QA audit schedule for investigator-initiated interventional trials can be found in the MBRCC DSMP. As appropriate the Biostatistics Core Facility will select a random number of charts for a retrospective review conducted by a team led by the Quality Assurance (QA) Specialist and varying number of independent support staff. All major protocol violations from internal and external QA audits are reviewed by the DSTC. The quality assurance process for case review audits includes review of:

- Informed Consent
- Eligibility
- Treatment
- Response
- Toxicities
- Adverse events
- Data completeness
- Pharmacy
- Regulatory documents

Scores are assigned to each review category deeming it sufficient, insufficient, or not applicable. Audit results will be reported to the PI, the DSTC and the Medical Director for Clinical Trials. In addition, components of quality assurance occur at various committees listed below:

- Specific Clinical Trials Disease Team
- Data Safety and Toxicity Committee
- Hematological Malignancy/Stem Cell Committee
- Early Phase I/II Committee
- Myeloma and Lymphoma Patient Care and Protocol Review Committee

High Risk Investigator-Initiated Trials Audit Process

Investigator-initiated trials that are deemed high priority by the PRMC for review and monitoring because of potential for increased risk (e.g., gene therapy, cell expansion, novel agents not previously administered to patients and use of experimental devices), will require first patient review/audits prior to further patient enrollment. In these instances, the QA Specialists recruits a team of two research nurses and one physician not associated with the protocol to

review the laboratory records, pharmacy records and treatment records to ensure that there is compliance with protocol guidelines, reporting procedures and toxicity reporting. Depending on the decision made, the trial may be modified or resume enrollment after this process is completed. At the point of continuing review (annual review as required per IRB guidelines), quality assurance on all therapeutic investigator-initiated trials will be performed to validate response and serious adverse events reporting accuracy by DSTC. Copies of the audits are kept in the CTRU Administration Office. Results are forwarded to the Clinical Trials Working Group for review/action, as well as to the study PI, the DSTC and to the IRB if protocol deviations are found. Enrolling physicians and study coordinators are both notified in writing as to the performance results of the case audit.

Study Coordinator Reviews

As part of the annual performance evaluation for all study coordinators, two charts are selected at random from accruals coordinated and managed in the previous year. These chart reviews are intended to serve as an evaluation tool for the study coordinator in terms of chart organization, timeliness of data submission and adherence to CTRU SOPs.

NCTNs

Cases accrued to NCTN protocols are subject to case evaluation, pathology verification, radiation port field quality control, and data query. The CTRU is reviewed on a three-year cycle by an independent review team from the NCTN on a randomly selected pool of accruals. NCTN trials are also subject to internal QA audits that examine a percentage of active trials at least annually. A goal of 10% of cases is given as 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.)

Industry Trials

The CTRU is subject to routine and regular monitoring by the sponsor (or the Clinical Research Organization) on pharmaceutical-supported trials. These records or reports when provided by the sponsor are retained in the CTRU Administrative Office and audit findings communicated to the DSTC. These studies are also subject to internal QA audits that examine a percentage of active trials for each Disease Team, as determined by the PRMC.

Laboratory Correlative Trials

Oversight for validation of lab correlate collection and reporting is under the jurisdiction of the PI, the assigned study coordinator, the Clinical Trials Disease Team, the appropriate Scientific Working Group, and/or the Cell and Gene Therapy Subcommittee. For investigator-initiated trials, a separate review group within the CTRU may be assigned to review all laboratory-based data for accuracy, protocol compliance and release criteria, as specified in the protocol. This is especially the case for early phase trials such as those involving, gene therapy, *ex vivo* cell expansion and early use of new drugs for which toxicity has not been established. Validation of

laboratory parameters is reviewed by the PI with the help of the Biostatistics Core Facility and reported to the appropriate Team.

B. EXTERNAL AUDIT PROCEDURES

Audits may be on-site or off-site via records review. Audits include:

- Regulatory information/documents (Form 1572 includes all sites of performance, sub-investigators, regulatory binders, laboratory certifications/normals, CVs, medical licenses etc.) and database review of regulatory information
    - IRB submissions/approvals
    - Documentation of all continuing reviews
    - Documentation of all amendment approvals
    - Changes in the informed consent document, if indicated
    - Review of timeliness of IRB submissions
    - Review of adverse event submissions to IRB
- Consent forms
    - Signature obtained on current IRB approved consent form prior to enrollment
    - Initial pages as appropriate
    - Documentation of consent process
    - Obtaining re-consent and documented, as indicated
- Patient charts are audited for protocol compliance items including:
    - Eligibility
    - Determine whether all concomitant therapy and /or intercurrent illnesses were included on the CRFs
    - Completion of procedures
    - Administration of treatment
    - Reporting correctly all toxicities – were appropriate interventions/modifications to subsequent dosing followed?
    - Documentation of response
    - Follow-up, data collection, record keeping is in order and plans in place for continued participation
    - Collection and submission of samples for correlative studies
- Investigational drug audit including DARF (Drug Accountability Reporting Forms) review for all sites. The intent is to verify:
    - Receipt date and quantity
    - Dates and quantity dispensed together with the identity of recipient (whether distributions was limited to study participants)
    - Whether quantity, frequency, duration, route of administration matches Case Report Forms (CRFs) and source documents
    - Date and quantity returned to sponsor or alternate disposition

- Determine proper storage maintained

X. DATA ANALYSIS AND REPORTING

A. BIOSTATISTICAL SUPPORT

The Mary Babb Randolph Cancer Center has entered into a collaborative partnership with the Department of Biostatistics in the WVU School of Public Health to provide devoted biostatistical support to MBRCC researchers. The MBRCC Biostatistics Core works with investigators in the analysis, reporting, and publication of study results. The Biostatistics Core extracts data from clinical trials databases, which then are imported into statistical packages (such as R/Bio conductor, or SAS) for statistical analysis.

Clinical trial analyses performed by the MBRCC Biostatistics Core range in complexity from simple descriptive summary statistics, to inferential statistics for testing hypotheses and parameter estimation, to more complex designs such as multi-stage phase II trials or analysis of studies with group-sequential interim analysis plans.

The policy of the MBRCC Biostatistics Core is to develop a detailed design and analysis plan for each trial (usually at the time of concept or Letter of Intent (LOI) stage of protocol development) as part of the study protocol, and reviewed again prior to the time when data analysis begins. This includes the determination of the sample size for achieving a specified power at a specified significance level. This will depend on the choice of a clinical endpoint as well as the clinically meaningful difference.

More completely, the Biostatistics Core Facility is responsible for clinical trial activities such as:

- Study design
- Dynamic, interactive data visualizations
- Statistical analyses
- Results reporting and publication displays
- Manuscript preparation

The Core activities span the basic and clinical sciences as envisioned by NIH's clinical and translational awards. These include nonclinical development (drug discovery, statistical quality control, quality assurance, etc.), preclinical development (in vitro assays, animal studies for toxicity and bioavailability, efficacy, etc.), and clinical development (phase I and II and eventually phase III trials). Biomarker development is critical for clinical studies and involves variable screening, model selection, and validation. Biomarker assays can be qualitative (SNPs), semi-quantitative (e.g., cDNA gene arrays and protein arrays), and quantitative (e.g., ELISAs and LC/MS).

Dr. Sijin Wen, Assistant Professor in the Department of Biostatistics and member of the

MBRCC (siwen@hsc.wvu.edu), leads the MBRCC Biostatistics Core. Dr. Wen received his PhD in Biostatistics at The University of Texas Health Science Center in Houston (2009). He previously was a Principal Statistical Analyst at MD Anderson Cancer Center from 2001- 2012. Dr. Wen has participated in the design and analysis of numerous clinical trials, laboratory experiments, and observational studies. He has extensive skills with simulations for clinical trial designs. His research interests include adaptive designs, interim analysis on efficacy and toxicity in clinical trials for cancer patients, multiple disease recurrences, multivariate survival analysis, and various applied statistical problems. In addition, Dr. Wen is interested in analyzing gene expression data from microarrays, protein arrays or tissue arrays, using clustering algorithms and statistical modeling. He has implemented algorithms and tools for analyzing high-throughput data sets. These analyses identify sets of genes that can be used to distinguish features between normal tissue versus cancer; different types or stages of cancer; or treated versus untreated cancer cells.

Dr. Wen had served as the primary statistical analyst on several NIH/NCI funded grants and clinical trials including NCI Specialized Program of Research Excellence (SPORE) in prostate cancer and genitourinary cancer, and Clinical & Translational Science Award (CTSA). His extensive contribution to statistical and cancer research has resulted in more than 80 published articles in both statistical journals such as Biometrics and cancer research journals such as Journal of the National Cancer Institute and Journal of Clinical Oncology.

In addition to Dr. Wen, Gerald Hobbs, PhD, Adjunct Associate Professor of Statistics, (ghobbs@stat.wvu.edu) also assists the Dr. Wen with the needs of the MBRCC.

Investigators are encouraged to utilize the MBRCC Biostatistics Core at the first stages of study design (e.g., concept or LOI), and to maintain an ongoing collaboration throughout the study, leading to final analysis and reporting of results. The email addresses are given above so that members can be contacted directly.

B. STORAGE OF RESEARCH DATA FOR INVESTIGATOR INITIATED STUDIES

Data security and integrity are essential to all research projects involving human subjects. A systematic approach across individual laboratories, offices and core labs will ensure institutional compliance and transparency with both regulatory agencies and formal queries by external auditors. Utilization of the OnCore® database for storage of clinical research data is strongly encouraged, including the insertion of any data generated from labs that will potentially be used for external reports or publications. If alternative means are taken, appropriate security measures, as outlined in this document, are important.

Protocol Elements

All investigator-initiated protocols involving human subjects should have a clear plan for acquisition, storage and access of data. This description should include both physical documents (e.g. case report forms) as well as electronic records.

Types of Data

Any data emanating from research with humans that are linked to protected information/identifiers are subject to the policies described in this Section. These data include information derived from the clinic (e.g. sex, weight, smoking history, etc.) as well as those derived from patient specimens (e.g. concentrations of a drug in plasma.)

Protected Information

Protected information consists of data such as the patients' name, medical record number, diagnosis, address, telephone numbers, DOB and medical history. Access to this information should be limited to those formally involved in the project, its analyses and those overseeing such.

Non-Protected Information

Core labs generate and maintain documents that are vital to compliance with clinical research projects, yet do not include any patient specific information (identified nor de-identified.) Examples of such may consist of temperature logs for freezers, equipment calibrations, assay validation documents, reagent lot logs, etc. It is important for such information to also have reliable storage and backup as delineated below under Storage Conditions.

Storage Conditions

It is strongly suggested that human data collected as part of an investigator-initiated clinical trial be stored in the OnCore® database, however if an alternative location is utilized, it is recommended the files reside on a centralized, limited access and protected database. In addition, researchers must abide by the HSC IT end user security policies.

http://its.hsc.wvu.edu/policies/computer-support-end-user-network-security-and-support-services-policies/

Laboratory studies often generate terminal data that is then linked to demographic and/or clinical outcomes measures (e.g. half-life of a drug). Such potentially publishable or externally reportable data should reside in the same database as the data discussed immediately above.

Research labs may also have secondary data sets which are used to generate the reportable parameters (e.g. blood concentrations of drugs). Such data typically have links to a patient identifier and should reside on centralized and protected databases (e.g. limited access Excel spreadsheet on MBRCC network data server) in a folder created by the Lab manager or PI. Data stored on the data server is backed up each night. In addition, backup files are replicated to a secondary server in another location.

Primary data produced in a lab (e.g. peak heights from a chromatogram) do not typically have direct patient identifiers and will often be saved on instrument-dedicated computers which may not be linked to the network or internet.

Access to Data

Access to the OnCore® database is provided to individuals based on their particular research role. The CTRU OnCore® Database Administrator is responsible for giving access privileges and monitoring database activities.

The individual lab director or study PI will determine who has access to research files through active directory permissions to the computer network system administrator.

XI. FEE STRUCTURE

Outlined below are the essential components of a fee structure that are utilized for clinical trials. The individual fees will vary among protocol requirements of the Mary Babb Randolph Cancer Center.

A. BIOSTATISTICS CORE FACILITY

Investigators are encouraged to utilize the Core Facility at the first stages of study design, and to maintain an ongoing collaboration throughout the study. Investigators are encouraged to involve statisticians of the Core Facility as collaborative co-investigators in their research projects.

Initial Consultation	no charge
Regular Consultation	costs will vary
Per Protocol Charges Trial Design Protocol development Sample size & statistical power calculations Database development CRF forms design	costs will vary
Analysis Statistical analysis Data processing Presentation of results Manuscript preparation	costs will vary
Per Patient Charges	cost will vary
Database management & reporting	costs will vary

B. CLINICAL TRIALS RESEARCH UNIT

The CTRU Administrative Office develops budgets for all industry-sponsored protocols and for all investigator–initiated protocols for which industry support is being sought. Budgets generally include both per patient costs and a one-time protocol development and initiation fee designed to cover investigator, CTRU, Biostatistics Core Facility, and administrative costs involved in the development, review, and initiation of the protocol. Per patient costs include physician protocol development, initiation, and assessment time; research nurse/coordinator and data management time; costs for the research-related tests and procedures; biospecimen acquisition/processing costs; pharmacy costs for dispensing the drug; administrative costs and appropriate overhead. Budgets for trials supported by NIH grants are reviewed and approved by the WVU Office of Sponsored Programs at the time that the grant is submitted.

The fee structure below outlines administrative fees that are incorporated into the budget(s) of physician investigator-initiated clinical research trials sponsored by pharmaceutical companies. These fees are in addition to administrative support for CTRU personnel and protocol-specific research expenses. The administrative charges are guidelines and negotiable as appropriate.

Budgets for federally-sponsored clinical trials are usually more fully developed.

Administrative charges for physician investigator-initiated trials:

- **PI Protocol Development and Initiation** **costs will vary**

  Covers time spent by PI in the development of the trial, review of the trial by CTEP or other agencies and in negotiations with the pharmaceutical company regarding support. Includes time spent evaluating patients and preparing for and participating in site initiation visits.

- **Research Nurse/Coordinator Protocol Development and Initiation** **costs will vary**

  Covers time spent by the research nurse/coordinator in reviewing the protocol to ensure that all required research-related resources including the CTRU Administration is aware of any research-related tests and procedures that need to be included in the budget. Includes time spent preparing for and participating in site initiation visits.

- **Administration Protocol Development and Initiation** **costs will vary**

  Covers time spent by CTRU Administration in developing and negotiating the budget and in facilitating review of the Clinical Trials Agreement (CTA) by the Office of Sponsored Programs at WVU.

- **Regulatory Review** **costs will vary**

  Includes time spent by the CTRU Regulatory Office in submitting the protocol for review by CTEP, making required modifications and resubmitting; developing informed consents, submission of protocol to the appropriate Scientific Disease Team, the Protocol Review and Monitoring Committee and the IRB.

- **Amendments or IRB Continuing Review** **costs will vary**

  Invoices are submitted as appropriate to cover costs of submitting amendments and continuing reviews to the IRB.

- **Biospecimen Processing Core Start-up Fee and Processing Charges** **costs will vary**

  The start-up fee covers administrative support to develop the protocol and set up the resources of the Biospecimen Processing Core (BPC) to handle the intended laboratory correlative studies. This requires protocol and lab manual review as well as creating instructions used by nurses and lab personnel for collecting, processing, analyzing, and shipping samples. In addition, BPC personnel attend start-up meetings and resolve issues related to missing or incomplete sample handling instructions.

- **Data Safety and Toxicity Committee (DSTC)** **costs will vary**

  Covers cost of review and documentation of all serious adverse events by the DSTC and their monthly meetings.

- **Investigational Pharmacy Review and Set-up** **costs will vary**

  Covers cost of review of protocol by investigational pharmacist to ensure appropriate shipping, maintenance and administration of the investigational agent.

- **Investigational Pharmacy** **costs will vary**

  Preparing and dispensing investigational drugs; maintaining inventory logs; randomization procedures if required; inpatient vs. outpatient.

- **Travel Expenses** **costs will vary**

  To cover travel expenses including round-trip airfare, ground transportation, registration fees, meals and lodgings for PI to attend one meeting to present results.

- **Publication Charge** **costs will vary**

  To cover expenses to prepare manuscript for publication including figures, photographs, photomicrographs, page charges, postage and shipping, reprints, other miscellaneous expenses.

- **Indirect Rate Charge** **26% off Campus**

- **Radiology Charge** **Cost will vary**

  The Radiology Department has agreed to provide professional services that affects the data collection for each appropriate protocol. This effort is above the customary professional associated routine radiological reads.

APPENDICIES

Appendix 1 – Data Safety and Monitoring Plan

http://www.hsc.wvu.edu/media/7804/dsmp-v2-final-012016.pdf

Appendix 2 – Instructions for Collaborating Institutions

Instructions for Collaborating Institutions

These procedures apply to both NCI sponsored and to non-NCI sponsored collaborating site studies sponsored by the MBRCC.

DEFINITION OF INSTITUTIONAL RELATIONSHIPS

For purposes of the oversight of conduct of cancer clinical trials, the following relationships are operative for the MBRCC:

Affiliate institutions are medical facilities within WVU Medicine (currently includes cancer centers at Camden Clark Medical Center, United Hospital Center and WVU Medicine Berkeley Medical Center).

Collaborating institutions are those medical facilities that collaborate for the conduct of specific clinical trials. In most instances the lead institution for a clinical trial will be the institution of the PI of record. All other institutions will be considered the collaborating institutions.

MBRCC Contacts:

CTRU Manager Oncology Services:	Anne Ness, RN, BSN CCRP 304-293-2745 abness@hsc.wvu.edu
CTRU Director	John Naim, PhD 304-293-4944 jnaim@hsc.wvu.edu
CTRU Interim Medical Director	Michael Craig, MD 304-293-4229 craigm@wvumedicine.org
CTRU Accountant	Joseph Brunetti, BS 304-293-7360 jbrunetti@hsc.wvu.edu
CTRU Network Coordinator:	Yvonne Shaw, MA 304-293-6251 yshaw@hsc.wvu.edu

Requirements to Activate a Collaborative Site

The collaborating institution is expected to provide the following documentation to the MBRCC Clinical Trials Research Unit (CTRU):

- Regulatory Documentation:
    - Institutional Assurances of Compliance (the current OHRP Project Assurance number (or FWA) for the institution and effective date(s))
    - Form FDA 1572 - This must be signed and dated by the Principal Investigator. In addition, all sub-investigators (if any) who are participating in the study, must be listed

on the form. All performance sites (including laboratories) must also be listed. The 1572 must be updated as medical staff and labs are added or deleted.

- Curriculum Vitae - A current copy is required for both the PI and each sub-investigator of the site. The front page must be signed and dated. A CV must be current each year, and should be replaced prior to expiration.
- Protection of Human Subjects Certificate or proof of completion is required for each PI, sub-investigator, and key personnel, renewed every 3years.
- Financial Disclosure Form - A signed and dated copy for each PI and sub-investigator is required (May use form FDA-3455)

- The name and address of the PI at each site must correspond to the cover sheet of the protocol in order for the site to obtain drug from the Pharmaceutical Management Branch (PMB) of CTEP.
- Laboratory Compliance Materials:
  - Copies of the CLIA and College of American Pathologists (CAP) certificates.
  - Copy of the normal ranges of laboratory values with corresponding units.
  - These materials are required of every laboratory used in the conduct of this study, and each laboratory should be listed on the Form 1572.
- Protocol Specific Requirements:
  - Copy of the IRB approval - Please refer to **IRB Submission Summary** section for details.
  - IRB approved informed consent A copy of the site specific informed consent must be reviewed and approved by the MBRCC Principal Investigator or designee. The consent form will be reviewed for content and also to confirm the presence of a statement that the research is being done in a multi-institutional setting, and that the Clinical Trials Research Unit will have access to confidential information and identified patient/study records.
  - The consent must follow the Code of Federal Regulations, which includes:

    1. A statement that the study involves research, and is multi-center
    2. The purpose of the study
    3. Description of the procedures and/or treatment
    4. Procedures to be performed to monitor the patients
    5. Risks/discomforts
    6. Benefits
    7. Alternatives
    8. Confidentiality statement which includes oversight by state and federal authorities as well as the MBRCC designated study staff

9. Compensation for study related injury clause
10. Emergency treatment or injury will or will not be provided
11. Contact person for research questions
12. Voluntary participation statement
13. Cost statement
14. Signature line

New Protocol Distribution, IRB Submission and Continuing Renewals

Once the MBRCC's final IRB approval has been received by the MBRCC CTRU Regulatory Office, the MBRCC will distribute the protocol and the consent form to the PI of the designated collaborating institution. Upon receipt of the materials, that institution is expected to confirm receipt and affirm their desire to participate in the trial. This should be done by email as promptly as possible.

If the collaborating institution decides that they do not wish to participate in a trial, the collaborating PI is requested to notify the MBRCC PI as well as the MBRCC CTRU.

The collaborating institution is expected to submit the protocol to their respective IRB (if applicable) as soon as possible after receipt. If a site chooses not to submit the protocol immediately, the site is encouraged to contact the MBRCC CTRU Regulatory Office prior to IRB submission, so that the most current version of the protocol and consent are made available.

The protocol's version number and date and/or amendment number and date must appear on the collaborating institution IRB approval letter. The version number and date are located on the face page.

The collaborating institution submits their IRB approval letter together with their approved consent form to the MBRCC CTRU Regulatory Office.

Site Initiation

Once IRB approval, consent approval, and regulatory data have been reviewed and accepted and a site initiation call will be arranged. This call includes the MBRCC PI, Network Coordinator, and the Research Nurse/Coordinator, Data Specialist and any other associated CTRU staff, together with the research staff from the collaborating site. The purpose of the call is to review the protocol requirements, answer questions, as well as review data expectations. The site will also receive written instructions as to data expectations, conference calls and study conduct; phone/fax number(s) of the MBRCC CTRU research staff is also provided.

Once the regulatory packet has been completed, the IRB/consent approvals received and accepted and the site has received the initiation call, the MBRCC CTRU Regulatory Office will

notify the PI of the collaborating site in writing that the trial is open for enrollment at their site. (Please refer to the section re: Requirements to Activate Collaborating Site).

Continuing Renewals/IRB Submission

The collaborating site will send a copy of their IRB continuing renewal approvals and consent changes/updates to the MBRCC CTRU Regulatory Office on an ongoing basis.

Amendment Distribution and IRB Submission

Once the sponsor and the WVU IRB have approved a protocol amendment, the Regulatory office of the MBRCC CTRU will send the amended protocol and consent form as applicable, to the collaborating institution. Upon receipt of the new version, the collaborating institution will do the following:

- Confirm receipt of the amendment, preferably by e-mail and as promptly as possible.
- Submit a revised consent form if applicable to the MBRCC Regulatory Office for review before IRB submission
- Submit to the collaborating institution's IRB as soon as possible after receipt. The amendment must be IRB approved by the institution within 90 days from the date that it was received.
- A copy of the IRB approval (and amended consent form if applicable) must be sent as soon as possible to the MBRCC CTRU Regulatory Office.
- The protocol version number and date and/or amendment number and date must appear on the IRB approval letter. The date should be located on the face page of the protocol. The approval letter should reflect whether the protocol (only) has changed, or if there are other changes such as revisions to the consent form. See IRB Submission Summary section for details.

Study Conduct

All PIs, sub-investigators, and research team members should have knowledge of **Good Clinical Practice (GCP)** and apply it to their participation in all clinical trials. It is recommended to follow CITI GCP training but documentation of other GCP training initiatives is acceptable.

All study records should be stored in a secure and safe facility with limited access until notified by the MBRCC CTRU that records retention is no longer necessary.

Key personnel should be available for periodic, scheduled conference calls to discuss the patients, toxicity, dosing issues, etc. Attendance on the calls is expected to be no less than 75%. Minutes of the calls will be distributed to the sites.

It is expected that proper control of drugs and/or biologics with respect to distribution and disposition be adhered to. If NCI-sponsored all NCI drug guidelines must be followed.

In order to maintain uniformity, it is the responsibility of the MBRCC's Data Safety and Toxicity Committee (DSTC) to review all responses. Arrangements to bring cases to the DSTC are to be made through the MBRCC CTRU research nurse/coordinator. Confirmation of response by the DSTC is conveyed in writing to the collaborating member as well as to the PI at MBRCC.

Key personnel should be available for periodic on-site audits by the MBRCC CTRU or any/all regulatory agents(s). It is possible that source documents will be requested by the MBRCC CTRU or other regulatory bodies for remote audit. All sites will be notified at a minimum of 30 days prior to an audit.

Patient Registration

- The collaborating institution must first have written permission to enroll patients into the trial. The notification will be sent to the PI of the collaborating site as soon as all required regulatory information has been accepted by the MBRCC CTRU.
- The collaborating institution must submit to the QA Specialist the following documents to begin the registration/randomization process:
    - the dated and signed informed consent form
    - a physician signed eligibility checklist
    - all source documents that validate eligibility
- Confirmation will be sent to the site (via email) once the patient has been enrolled into the study to issue the unique patient identifier and the dose/level/cohort as applicable.

Data Acquisition and Submission

- Informed consent, including HIPAA authorization, must be obtained on all subjects prior to their participation.
- Always keep the original signed and dated consent form, sending a copy to the MBRCC CTRU with the source documents and eligibility checklist. A physician must sign the checklist confirming eligibility and intent to register the patient.
- In the event that the consent is signed, but later is either withdrawn or inactivated- even if the patient did not begin treatment- send a copy of the signed and dated consent to the MBRCC CTRU.
- Case report forms will be provided by the MBRCC CTRU specific to each study. This may be by paper CRF's or electronic data capture through the OnCore® database.
- Data submission is expected according to schedule in the protocol.
- For paper CRF's:

- Please submit original forms, done in black or blue ink written legibly or typed.
- Amended data should be identified as such, and the change(s) written in red ink, initialed and dated.

• The source documentation for each subject should be clearly written/typed, dated and signed; all printouts, test reports, and procedures should be signed and dated.

• Baseline and on-study forms are due within 6 weeks of registration. Please use the date of registration as the On-Study date.

• Source documents include, but are not limited to:

- Medical records
- Chemotherapy treatment records/notes
- Radiation treatment records/notes
- Laboratory/pathology reports
- Radiology reports
- EKGs, MUGA, etc. reports
- Correspondence related to patient care
- Home care documents

Serious Adverse Event Reporting

- The MBRCC CTRU regulatory office must be notified of any serious adverse event that requires expedited reporting within 24 hours of discovery of the event. The appropriate written report should be submitted as soon as possible directly to the sponsor following written guidelines of the protocol, and to the MBRCC CTRU. This can be done by notifying the Network Coordinator, Oncology Manager or the MBRCC PI.

- The MBRCC PI or designee should receive a copy of the official report simultaneously with the submission to the sponsor and the collaborating institution's IRB per protocol and local IRB guidelines

- All reports should include:
  - Protocol number
  - Pt study ID
  - Lead Investigator
  - Treating MD
  - Date of the event
  - Last date of treatment

- Description of the event, include intervention(s)
- Outcome – if not resolved, submit a follow-up
- Grade and Attribution for each toxicity and each agent

- Upon receipt the report will be submitted to the MBRCC DSTC and distributed to all other affiliate institutions.
-
- Collaborating Institutions must submit external SAE reports received from other affiliate sites to their respective (local) IRB.

For NCI sponsored trials:

• NCI expedited reporting requirements must be followed. While each protocol dictates specific guidelines for reporting toxicities, and may state exceptions, they usually follow the CTEP-AERS guidelines. CTEP-AERS can be reached via the website: http://ctep.cancer.gov.

Reporting Deaths

Deaths occurring while on treatment or after treatment is completed but prior to 30 days should be reported within 24 hours regardless of attribution.

Deaths occurring greater than 30 days after the last dose of treatment that have an attribution of possible, probable or definite, should be reported within 24 hours of notification.

Audits

Audits may be on-site or records may be requested which will include copies of the source documents. Audits will include:

• Investigational drug audit including DARF (drug accountability reporting forms) review for all performance sites. The intent is to verify:

- Receipt date and quantity
- Dates and quantity dispensed together with the identity of recipient (whether distributions were limited to study participants)
- Whether quantity, frequency, duration, route of administration matches CRFs and source documents
- Date and quantity returned to sponsor or alternate disposition
- Determine proper storage maintained

• Consent forms

- Signature obtained on current IRB approved consent form prior to enrollment

• IRB approvals

- Initials
- Documentation of all continuing reviews
- Documentation of all amendment approvals
- Changes in the informed consent document if indicated

• Regulatory information (Form 1572 includes all sites of performance, sub-investigators, etc.)

• Patient charts are audited for protocol compliance items including;

- Eligibility
- Determine whether all concomitant therapy and /or inter current illnesses were included on the CRFs
- Completion of procedures
- Administration of treatment
- Reporting correctly all toxicities--Were appropriate interventions/modifications to subsequent dosing followed?
- Documentation of response
- Follow-up, data collection, record keeping is in order and plans in place for continued participation
- Collection and submission of samples for correlative studies.

Summary of IRB Related Submissions from Collaborating Institutions to the MBRCC CTRU

Please submit the following to the MBRCC CTRU Network Coordinator for each trial:

Initial Submission

• Please provide the protocol version number and version date and/or amendment number and date (located on the front page of the protocol document) on your IRB approval letter.

• A copy of the new consent form *is* required.

• REMINDER: If this is an NCI-sponsored trial, you must fax a copy of the approval to the PIO @ (301) 496-9384. Drug will not be dispensed by the NCI without a copy of your approval.

Protocol Changes *Only* (NO consent form change)

Please provide the protocol version number and version date and /or amendment number and date on your approval letter.

• Since there is no consent change, the consent does *not* need to be sent.

Consent Form Changes *Only* (Protocol version remains unchanged)

- Please provide the protocol version number and version date and/or amendment number and date on your approval letter.
- Please provide a statement that the consent form has been modified.
- A copy of the new consent form *is* required.

Protocol *and* Consent Form Change (NOT initial submission)

- Please provide the protocol version number and version date and/or amendment number and date.
- Please provide a signed statement that both the consent form and the protocol were modified.
- A copy of the new consent form *is* required.

Collaborating Site Instructions for Conducting NCTN Studies

Version date: October 2015

Collaborating Site Activation Requirements:

- **Clinical Faculty Appointment** - All physicians must apply for a Courtesy Clinical Faculty Appointment through the West Virginia University School of Medicine. Approval of this appointment is mandatory for participation in clinical trials as outlined in the Memorandum of Understanding between the WVU Research Corporation and the Collaborating Site. Completed applications must be submitted to the Research Network Coordinator. Courtesy Clinical Faculty Appointments are required to be renewed on an annual basis. Site staff will be contacted regarding this reappointment via the WVU School of Medicine.
- **CITI Training** - All members of the research team and other key personnel at the collaborating site must complete the CITI human subject research training course titled "Biomedical Research Investigators" and the CITI Conflicts of Interest Training course; both courses can be located on the CITI website at https://www.citiprogram.org/. Training must be completed prior to the activation of studies at the collaborating site. This requirement applies to any new research team members added to any study whether it is actively enrolling or closed to enrollment. Research team and key personnel includes but is not limited to investigators, study coordinators, data managers, pharmacists, and regulatory staff. The site's Institutional Review Board may require specific training modules that will need to be completed in addition to the aforementioned requirements.
- **NCI Registration** - Physicians at collaborating sites must also be registered with the National Cancer Institute's Pharmaceutical Management Branch. The forms needed to register a physician are found at http://ctep.cancer.gov/resources/investigator2.html. A copy of the completed NCI registration forms must be submitted to the Clinical Trials Research Unit (CTRU). The CTRU does not require copies of the annual renewal forms, but encourages the site to keep these in a central file within their institution. Physicians will not be permitted to enroll patients or order study drug if this registration is not kept active (yearly basis). All NCI Investigator Numbers will need to be provided to the CTRU.
- **CTEP ID Number** - Each member of the research team (physicians and non-physician research staff) is required to obtain a CTEP (Cancer Therapy Evaluation Program) identification number. A unique, active email address is required. For investigators, the CTEP identification number is the same as their NCI registration number, but they will still need to register with CTEP. For access to this registration process visit the following web site: https://eapps-ctep.nci.nih.gov/iam. A CTEP-IAM Fact Sheet that provides a brief outline of the process is available at https://members.ctsu.org/CTEP-IAM_FactSheet.pdf.
- **Federal Wide Assurance Number** - Collaborating sites must obtain and provide their local IRB Federal Wide Assurance number to the Clinical Trials Research Unit. The Federal Wide Assurance number application can be found at the following website:

http://www.hhs.gov/ohrp/assurances/forms/fwainstructions.html. Additional training may be required per OHRP guidelines.

- **Institutional Authorization Agreements** must be implemented prior to the activation of studies at the collaborating site. The IAA allows the NCI CIRB or WVU IRB to serve as the "IRB of Record" for protocols and stands as a written agreement to allow the IRB to review, approve and oversee human subjects' research on behalf of the other institution.
- WVU CTRU will confirm NCTN affiliation and update rosters appropriately.
- Sites are encouraged to implement the WVU Eligibility Verification Policy. Training will be provided to the site's research staff regarding this policy, if desired.
- Contact information for research team members for each study must be provided to the CTRU, especially the designated Study Coordinator for each study. Please provide a phone number, email address, fax number and pager number/mobile phone number.
- Additional information may be required depending on individual protocol specifications.

Upon study activation at collaborating site:

- Collaborating sites will be utilizing the NCI CIRB for NCTN sponsored trials when available. If the trial is not a NCI CIRB trial then the sites will need to submit to the WVU IRB or local IRB of record. The WVU CTRU will submit on behalf of all NCTN affiliate members to the appropriate IRB of record. If the site has an additional local IRB, the Study Coordinator at the site will need to submit.
- All IRB reviews and approval, including documents, will be available to the sites via OnCore®.
- Once a collaborating site is established and open to accrual, monthly teleconferences between the WVU CTRU and the collaborating site shall be conducted. The monthly teleconferences will aid in maintaining an open line of communication between the institutions where protocol updates, staff changes and general questions regarding clinical trials may be discussed. The WVU CTRU requests that at least the collaborating site's Principal Investigator and Study Coordinator join these monthly teleconferences. All other essential study personnel are welcome to attend.
- Data will be monitored by the Network Coordinator and/or QA Specialist using the NCTN generated delinquency reports. Excessive and repeat delinquency problems will be addressed according to the NCTN operating procedures.
- Monitoring visits will be scheduled based on accrual and site performance.

Appendix 3 - PRMC Forms

1. **PRMC Submission Form (Disease Team Signoff Form)**
2. **PRMC Non-Treatment Submission Form**
3. **Coordinator Review Form**
4. **Protocol Review Form – Investigator Initiated**
5. **Protocol Review Form – Industry**
6. **Pharmacy Review Form**
7. **Biostatistician Review Form**

WVU Cancer Institute
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PRMC Protocol Submission Form

To be completed by Disease Team

PROTOCOL NUMBER/TITLE: _____

This protocol was presented, discussed, and accepted at the _____Disease Team meeting on _____

Signed: Disease Team Leader_____ Date: _____

---

1. Is there advocacy for this trial? YES _____ NO _____

If NO, it is not necessary to complete Questions 2.

If YES, is there a competing study? YES _____ NO _____ If YES complete item 2.

2. If YES to competing study, please prioritize accrual to a study number

1) highest priority (1st for accrual) _____ study name
2) high priority (2nd for accrual) _____ study name
3) priority(3rd for accrual) _____ study name

Comments:_____

Projected 1-year accrual goal from time of activation: ___ patients Estimated time of accrual _____months

Priority Scoring System: **1**-Outstanding, **2**- Excellent, **3** - Good, **4** - Acceptable, **5** - Not Scientifically Meritorious

Note: Best score for pharmaceutical and cooperative group trials is 3- Good

Disease Team's
Scientific Priority Score: _____ Comments _____

Participating Facilities: □ MBRCC □ MBRCC Affiliates □ Other_____

To be completed by Principal Investigator

PI Conflict of Interest: To be completed by PI/Study Chair.
Defined by WVU Conflict of Interest in Research policy. (see http://oric.research.wvu.edu/conint)

□ I have no financial interest(s) in the sponsor(s) of this study

□ I have financial interest(s) in one or more sponsor(s) of this study. Please elaborate using a separate sheet.

Signed: _____ _____ Date:_____
PI/Study Chair Print Name

Investigator-Initiated Trials

Has a study budget been drafted with CTRU input? □ YES □ NO

If YES, please attach budget.

If NO, please contact CTRU Director for guidance at 304-293-4944

Has funding been secured to support the entire study? □ YES □ NO

If YES please provide name of sponsor_____

If NO, has a funding source been identified □ YES □ NO

If YES, please provide expected date when funds will be available _____Date

If NO, please contact Cancer Center Director's Office for guidance

***Studies involving an intervention (e.g., drug, device, biospecimen sampling, etc.) will require an assigned CTRU Study Coordinator and a funding source prior to activation.**

WVU Cancer Institute
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PRMC – Protocol Review and Monitoring Committee Protocol Information Form

Use this form to submit Non-Treatment protocols to the PRMC (Chart Review, Survey, Questionnaire, etc.)

This form along with an abstract and protocol/research plan must be submitted to Laila Wallace at lwallace@hsc.wvu.edu or PO Box 9260 in order for the protocol to be put on the PRMC agenda. **Questions? Please call the CTRU at (304) 293-0692.**

General Protocol Information

IRB #:	
Full Protocol Title:	
Objective:	
Principal Investigator:	Name/Department: _____ PO Box: _____ Phone & Fax: _____ Email: _____
Study Coordinator:	
Sub-Investigator(s): ***Additional Sub-I(s)? List names below:**	Name / Department/Section
Sponsor/Granting Agency:	Sponsor Name: _____ Primary Study Contact ☐ CRO ☐ Sponsor ☐ Other Name/Title: _____ Phone: _____ Fax: _____ Email: _____

Study Type:
- ❑ Chart Review
- ❑ Survey
- ❑ Questionnaire

Other (Describe) _____

Study Duration: Projected Open Date: _____
Close Date: _____

Accrual Goal: _____

Patient Log form must be submitted at the end of the study or at the end of the calendar year, whichever occurs first, for annual accrual recording. (Chart reviews only need to report the number of charts reviewed)

WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

PROTOCOL REVIEW AND MONITORING COMMITTEE

RESEARCH COORDINATOR SIGN-OFF SHEET

The Mary Babb Randolph Cancer Center Protocol Review and Monitoring Committee received the proposed protocol:

Protocol Number: _____

Review the protocol and complete the items below. Turn in sheet prior to OnCore ePRMS submission.

Circle answer and comment as applicable.

Eligiblity				Comments:
Yes	No	N/A	Inclusion/Exclusion criteria clear	
Yes	No	N/A	Timeframe acceptable for screening procedures	
Yes	No	N/A	Do any of the eligibility criteria pose a barrier to meeting the proposed accrual goal	

Logistics and Reporting				Comments:
Yes	No	N/A	Are the time windows for study procedures clearly stated and adequate in regard to enrolling and/or treating the patient?	
Yes	No	N/A	Are the on-study/patient registration procedures clear?	
Yes	No	N/A	Study procedures to be conducted during normal working hours	
Yes	No	N/A	Any special scheduling requirements that may be difficult to comply with?	
Yes	No	N/A	Any of the trial requirements particularly onerous for the research staff (i.e. CRF completion, PK's, exams, etc.)?	
Yes	No	N/A	Any concerns regarding ancillary department's ability or willingness to comply with the protocol requirements?	
Yes	No	N/A	Will study procedures or administration of investigational product require additional time or dedication of resources from the MBRCC staff?	
Yes	No	N/A	AE and SAE reporting requirements clearly written in the protocol	
Yes	No	N/A	Tissue collection and banking issues addressed	

Patient Concerns				Comments:
Yes	No	N/A	Any of the study procedures particularly onerous for the patient (ie blood draws, extra biopsy, etc.)?	
Yes	No	N/A	Any ethical concerns?	
Yes	No	N/A	Are the study procedures that are NOT considered "standard of care" paid for by the sponsor?	
Yes	No	N/A	Do you anticipate any other additional costs to the patient that may not be covered by the sponsor (ie overnight hotel stay, travel costs secondary to frequent visits, etc.)?	
Yes	No	N/A	Does the consent form adequately describes the protocol and benefits and/or risks to the patient?	

Drug procurement and administration				Comments:
Yes	No	N/A	Are any of the medications involved in the study supplied by the sponsor? If yes, please list.	
Yes	No	N/A	Do you anticipate any financial issues?	
Yes	No	N/A	Any significant administration issues such as IV incompatibility to commonly used fluids, lengthy treatment, etc.?	

Any other issues or comments: _____

_____

_____

_____

Research Coordinator: _____ Date of Sign off: _____

WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

PROTOCOL REVIEW AND MONITORING COMMITTEE
REVIEWER SIGN-OFF SHEET
INVESTIGATOR INITIATED PROTOCOL

The Mary Babb Randolph Cancer Center Protocol Review and Monitoring Committee received the proposed protocol:

Protocol Title:

Principal Investigator: **Accrual goal:**

Review the protocol and complete the items below. Turn in sheet at the PRMC meeting.

Score each item using the scale: **1** = acceptable, **2** = not acceptable for reason noted, **3** = not applicable

Comments:

____ Objectives _____

____ Scientific Rationale and Merit _____

_____

____ Eligibility Criteria _____

____ Treatment Plan/Study Design _____

____ Measurement of Effect _____

____ Study Parameters/procedures _____

____ Patient Consent Form (if available) _____

____ Accuracy of accrual rate _____

____ Data Safety Monitoring Plan _____

____ Other comments _____

_____

Level of Risk to the patient:

___ **High** (e.g. novelty of therapy, investigator-initiated Phase I, first in humans, gene therapy, severe or life threatening side-effects)

___ **Moderate** (some clinical experience and appreciation of toxicity, moderate toxicity)

___ **Low** (clinical safety is generally well characterized, registries, correlative, behavioral health, etc.)

Is the DSMP described in the protocol, adequate for the level of risk to the patient? ___Yes __ No

If No, suggestions for DSMP _____

Scientific Priority Scoring System: 1-Outstanding, **2**- Excellent, **3** - Good, **4** - Acceptable, **5** - Not Scientifically Meritorious

Reviewer's Scientific Priority Score: _____ Comments: _____

Reviewer: _____ Date of Review: _____

WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

PROTOCOL REVIEW AND MONITORING COMMITTEE
REVIEWER SIGN-OFF SHEET
INDUSTRY SPONSORED PROTOCOLS

The Mary Babb Randolph Cancer Center Protocol Review and Monitoring Committee received the proposed protocol:

Protocol Title:

Principal Investigator: **Accrual goal:**

Review the protocol and complete the items below. Turn in sheet at the PRMC meeting.

Score each item using the scale **1** = acceptable, **2** = not acceptable for reasons noted, **3** = not applicable

Comments:

____ Objectives _____

____ Scientific Rationale and Merit _____

_____

____ Eligibility Criteria _____

____ Treatment Plan/Study Design _____

_____

____ Measurement of Effect _____

____ Study Parameters/procedures _____

____ Patient Consent Form (if available) _____

____ Accuracy of accrual rate _____

____ Data Safety Monitoring Plan _____

____ Other comments _____

_____

Is the DSMP described in the protocol, adequate for the level of risk to the patient? ___Yes __ No

If No, suggestions for DSTC monitoring_____

Scientific Priority Scoring System: Note: Best score for pharmaceutical and cooperative group trials is 3- Good

3 - Good, **4** - Acceptable, **5** - Not Scientifically Meritorious

Reviewer's Scientific Priority Score: _____ Comments: _____

Reviewer: _____ Date of Review: _____

WVU Cancer Institute
MARY BABB RANDOLPH CANCER CENTER

PROTOCOL REVIEW AND MONITORING COMMITTEE
MEDICATION CHECKLIST

The Mary Babb Randolph Cancer Center Protocol Review and Monitoring Committee has received the proposed protocol:

Protocol Title:

Principal Investigator: **Accrual goal:**

Investigational drug ☐ Yes ☐ No

Formulary ☐ Yes ☐ No

Study Supply Medication: _____

1. Is the medication provided free of charge? Yes ☐ No ☐
   Comments: _____

2. Are medications NOT provided free of charge being used per the hospital's guidelines for that drug? Yes ☐ No ☐
   Comments: _____

3. Are all drug preparations/dispensing/storage guidelines clear and according to the standard of care at the institution?
   Yes ☐ No ☐ Comments: _____

4. Drug acquisition: ☐ Clear ☐ Unclear
   Comments: _____

5. Drug availability following study: ☐ Clear ☐ Unclear
   Comments: _____

6. List of adverse effects: ☐ Clear ☐ Unclear
   Comments: _____

7. Can the study be extended to satellite locations? Yes ☐ No ☐
   Comments: _____

Additional Comments:_____

_____ Date _____
Lisa Giblin Sutton, PharmD

PROTOCOL REVIEW AND MONITORING COMMITTEE

STATISTICIAN SIGN-OFF SHEET

The Mary Babb Randolph Cancer Center Protocol Review and Monitoring Committee has received the proposed protocol:

Protocol Title:

Principal Investigator: **Accrual goal:**

1=acceptable; 2=not acceptable for reasons noted; 3=not applicable

		Comments
___	Objectives Addressed	_____
____	Appropriate Endpoints	_____
____	Appropriate Design	_____
____	Safety Monitoring/Dose Modification	_____
____	Sample Size Justification	_____
____	Screening Failures Accounted	_____
____	Data Analysis Methods	_____
_____	Overall Protocol	_____

_____ _____

Sijin Wen, Ph.D. Date
Gerald Hobbs, Ph.D.

Appendix 4 - Letters from the IRB

MEMORANDUM

Date: April 13, 2010

To: Scot C. Remick, MD
Director
Mary Babb Randolph Cancer Center (MBRCC)

From: Daniel R. Vasgird, PhD
Director, Office of Research Integrity & Compliance

RE: Review of Cancer-Related Protocols

This memo is to acknowledge that all cancer-related human subject protocols are reviewed and approved by the West Virginia University Institutional Review Board after review and approval for scientific merit by the MBRCC Protocol Review and Monitoring Committee.

Oversight for all cancer-related clinical research protocols involving human subjects including clinical, translational, population, psychosocial and prevention studies is the responsibility of the WVU IRB.

cc: Dr. Curt Peterson
Stephen Davis
Matthew Riegel
Dr. Christopher Colenda
Dr. James Brick
Lilo Ast

Phone: 304-293-7073
Fax: 304-293-3098
http://orc.research.wvu.edu/

Chestnut Ridge Research Building
886 Chestnut Ridge Road
PO Box 6845
Morgantown, WV 26506-6845

West Virginia University
Office of Research Integrity and Compliance

Memorandum

Date: May 14, 2010

To: Scot C. Remick, MD
Director
Mary Babb Randolph Cancer Center (MBRCC)

From: Daniel Vasgird, PhD
Director
Office Research Integrity and Compliance

RE: *Cancer Clinical Trials 101*

This memo is to acknowledge the *Cancer Clinical Trials 101* course held quarterly in the MBRCC clinic conference room provides contemporary information about regulatory guidance, research compliance, ethics of clinical trials, human subject protections, and general training about clinical trials conduct among other topics of importance as they arise. This venue will also provide an opportunity for review and self-reflection of our clinical trials research program(s), policies and procedures that are subjected to the myriad of reviews, audits and annual reporting that the Clinical Trials Research Unit (CTRU) participates in annually.

It is our understanding that an agenda is distributed prior to the conference; minutes are kept and distributed; attendance is recorded and mandatory (2 out of 4 conferences per year) for all clinical investigators and research personnel participating in our Cancer Center clinical trials program. The Office of Research Integrity and Compliance is prepared to recognize that participation in this seminar series devoted to clinical trials education is eligible for Continuing Research Education Credits (CREC) and our office is in the process of developing policies and procedures for on-going training in this area.

Thank you in advance for developing this novel continuing education program in the Cancer Center.

Cc: James Brick, MD
Christopher Colenda, MD, MPH
Jame Abraham, MD
Lilo Ast

Phone: 304-293-7373
Fax: 304-293-3398
http://oric.research.wvu.edu

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886 Chestnut Ridge Road
PO Box 6845
Morgantown, WV 26506-6845

Appendix 5 – Protocol Template

http://www.hsc.wvu.edu/media/7805/protocol-template-022016.doc

Appendix 6 – Guidance for Industry

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf