West Virginia Clinical and Translational Science Institute

CLINICAL RESEARCH OPERATIONS MANUAL

"The Gold Book"

Director for Clinical Research
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Introduction and Background

The policies and procedures in the second edition of the West Virginia Clinical and Translational Science Institute's Clinical Trials Operations Manual (hereafter referred to as the Gold Book) were adapted from the Mary Babb Randolph Cancer Center Clinical Trials Operations Manual (referred to as the Blue Book). The West Virginia Clinical and Translational Science Institute wishes to both acknowledge and thank the Mary Babb Randolph Cancer Center Clinical Trials Research Unit for their support and guidance as we continue to build our clinical research enterprise.

There are elements in the second edition of the Clinical Trials Operations Manual that are in the formative phases of development as our research mission and programs continue to evolve. 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 Clinical Trials Research Unit (CTRU) and scientific administrative positions are To Be Named, which are connoted by TBN. Subsequent editions of the Gold Book will capture these new requirements as they come online.

Revision one contains updated names and roles and the requirement for GCP training for all clinical HSC faculty and staff.

The Gold Book

The Gold Book provides a roadmap for the conduct of Good Clinical Practice (GCP) based clinical studies. It has been developed to provide transparency to the process of developing, executing and monitoring clinical and translational research projects uniformly throughout the State. Further it should help to facilitate the integration of research operations across WVCTSI participating institutions by standardizing policies and procedures for the conduct of clinical trials and population studies.

The clinical research operation manual (Gold Book) applies to all WVCTSI related clinical research not involving cancer patients. This manual applies to faculty participating in clinical research for all participating institutions conducted under the auspices within WVCTSI.

Abbreviations

AE	Adverse Event
CAP	College of American Pathologists
CDA	Confidentiality Disclosure Agreements
CITI	Collaborative IRB Training Initiative
CLIA	Clinical Laboratory Improvement Amendments
COI	Conflict of Interest
CRFs	Case Report Form(s)
CTRU	Clinical Trials Research Unit
CTWG	Clinical Trials Working Group
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendment Act of 2007
GCP	Good Clinical Practice
Gold Book	WVCTSI Operations Manual
HIPPA	Health Insurance Portability and Accountability Act of 1996
HSC	Health Sciences Center
IACUC	Institutional Animal Care and Use Committee
IDE	Investigational Device Exemption
IIT	Investigator Initiated Trial
IND	Investigational New Drug
IRB	Institutional Review Board
LOI	Letter of Intent
NIH	National Institutes of Health
NLM	National Library of Medicine
OHRP	Office of Human Research Protection
ORIC	Office of Research Integrity and Compliance
OSP	Office of Sponsored Programs
PI	Principal Investigator
SAE	Serious Adverse Event
SOC	Standard of Care
TBD	To Be Determined
TBE	To Be Established
TBN	To Be Named
WVCTSI	West Virginia Clinical and Translational Science Institute

I. Clinical Trials Working Group (CTWG)

The WVCTSI Director, the Vice President of Research and Graduate Studies, and the WVCTSI Assistant Director of Operations work closely with the Director of the CTRU. The CTWG Chairman is charged with establishing and maintaining CTRU research infrastructure, integration, and interfaces to support clinical trials and population research missions. The CTWG meets on a bimonthly basis and is composed of faculty and hospital leaders throughout the Health Sciences Center. The CTWG is committed to leading, building, and providing suitable resources for WVCTSI investigators to conduct highly interactive clinical trial and population research projects. In addition, the CTWG also facilitates research collaborations across partner institutions. In the WVCTSI, each partner institution organizes and centralizes their participant-oriented research activities under the CTWG umbrella to increase efficiency and provide a mechanism for regular and ongoing information about studies, investigators, and personnel. See Appendix 1 for a list of members.

Purpose

The main function of the CTWG is protocol review and monitoring. The CTWG is responsible for scientific review of investigator-initiated protocols. More specifically, CTWG is established to accomplish the following:

- To advise the WVU Institutional Review Board on the scientific merit of proposed protocols.
- To establish priority ranking for protocols.
- To ensure that each clinical trial or proposed study has an appropriate statistical section.
- To ensure that the data to be collected are appropriate to the study's goals.
- To monitor the progress of WVCTSI protocols.
- To activate approved research protocols.
- To recommend protocol closure to the appropriate Department/School leadership.

Criteria for Selection of CTWG Membership

The Director of Clinical Research appoints members of the CTWG. Ad Hoc members are added as dictated by the protocol therapeutic area. Clinical Trials Working group includes a balance of senior clinical investigators and new clinical investigators so as to foster the development of new researchers. Additional reviewers are asked by the CTWG to comment on specific protocols and to assist in the review of protocols in their area of expertise, as needed.

CTWG Expertise and Charge

The CTWG has sufficient breadth of expertise to allow objective and critical scientific review of all types of therapeutic, non-therapeutic and investigator-initiated clinical trials. The Committee includes experts from each of the respective sub-specialties that include: pediatrics, internal medicine, nursing, pharmacy, community medicine, behavioral sciences, laboratory correlative studies, biostatistics and patient advocacy. 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 CTWG is charged with review of the scientific rationale for the trial, establishing the priority relative to other clinical trials, 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.

Protocol Routing and Activation

Once the protocol has been reviewed and approved by the CTWG, the Clinical Trials Research Unit (CTRU) Regulatory Office is notified that the protocol is allowed to be submitted to the WVU IRB. If other approvals are required, such as those for cell and gene therapy protocols, the appropriate additional committee is apprised such as the Biosafety Committee, Radiation Safety Committee, etc. Simultaneously, Clinical Trials Research Unit (CTRU) coordinates other necessary documents that allow protocol activation. All protocols that involve patients placed on pharmacokinetic studies, research biopsies, etc., are reviewed and coordinated with the CTRU. Once each of the components of protocol approvals has been completed, this is reviewed by HSC administration and the protocol is signed off and activated by the Director for Clinical Research.

Selection Criteria for CTWG Membership and Interactions

Members of the CTWG are appointed by the Director for Clinical Research with consultation with the HSC Chancellor for a renewable 3-year term. Members are expected to participate in the semi-monthly committee meeting and provide focused expertise as needed in protocol review. In rare instances, the CTWG 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.

Guidelines for Operation

The CTWG meets semi-monthly. The meeting is chaired on a rotating basis by the Chair and co-Chairs; each is responsible for sign-off of final minutes for the appropriate session chaired. The CTWG Chair is responsible for overall coordination of the meeting and responding to or directing any inquiries. The assigned meeting Chair and co- Chair develop the meeting agenda, which is distributed a minimum of 3 days before each scheduled meeting. The Committee considers new concepts (LOIs) presented by individual investigators, reviews new protocols, and monitors the progress of active studies.

II. Protocol Review and Monitoring

Emphasis of protocol review and monitoring is placed on review of investigator-initiated institutional trials and investigations. Of greatest importance is the assistance the Clinical Trials Working Group provides investigators in the development of concepts that lead to successful activation of novel clinical research protocols. Guidance is also provided to those studies, which are prevention and behavioral intervention oriented. Investigators are encouraged to bring new therapeutics concepts or letters of intent to the CTWG for review. By the time these trials are reviewed, bio-statistical input has been provided through the WVCTSI Clinical Research Design, Epidemiology & Biostatistics Core

Facility faculty, and study coordinators have participated in the logistical operations development. The department Chair and/or Section Chief will have reviewed the concept or LOI for the availability of patients and for overlap in prioritization relative to other active clinical trials.

A. Protocol Concepts/LOIs Review

Before development of a formal protocol, investigators are encouraged to present the objectives of the proposed trial in the form of a concept/letter of intent (LOI) for review by the CTWG. The proposed trial will be discussed with the investigator present, from the following points of view: 1) scientific merit; 2) statistical methodology; 3) relationship to ongoing protocols; and 4) accrual goals. The potential funding source(s) for any particular concept/LOI is also identified (e.g., industry sponsor, etc.). Investigator-initiated clinical investigation is given highest priority by CTWG, since this is the primary level of physician investigator-initiated clinical investigation and provides an important venue to mentor new and junior investigators. Priority is also given to WVCTSI clinician scientists, scholars and pilot awardees. No formal action is taken by the CTWG on concept presentations. Formal LOI submissions are, however, fully reviewed and acted upon by the Committee.

B. Review of New Protocols

A CTRU service application, reviewer, statistician and study coordinator sign-off sheets, are used to facilitate the review process, see Appendix 8.

Prior to the CTWG review, two members are designated by the Chair or co-Chair to review each protocol. The CTWG review includes a biostatistician and pharmacy reviewers (as applicable). In general, the reviewers will be representative of the discipline appropriate for the protocol under review. The CTWG will make every effort to avoid assigning potential co-investigators as reviewers. The reviewers receive a complete protocol, informed consent document, and sign-off sheets 5 days prior to the meeting.

The Committee evaluates the scientific merit of proposed protocols, appropriateness of the target population, and appropriateness of patient care. The CTWG ensures that each clinical trial has an appropriate statistical section and a realistic accrual goal. The reviewing statistician is responsible for statistical sign-off.

For industry sponsored and multicenter nationally funded studies, the assigned study coordinator is responsible for logistical review and presenting the study at a convened CTWG meeting. The CTWG has the opportunity to ask questions and to assure that the study is feasible, CTRU resources are available and costs are covered by the sponsor. The PI is usually not required to attend this meeting, but is free to request attendance on a case by case basis. These studies are usually not subject to scientific review.

See CTRU protocol submission and activation schema on page 21.

Scientific Score and CTWG Recommendations

The CTWG assigns a scientific score, range 1.0 to 5.0: **5**-Outstanding, **4**- Excellent, **3** - Good, **2** - Acceptable, **1** - Not Scientifically Meritorious.

In addition the protocol is given a probability of funding score: **5** – High, **3 -**Medium, **1**- Low.

Overall score is the product of the two scores. An overall score of greater than 10 would be considered meritorious and score of 25 is the highest possible overall score.

CTWG may take one of the following actions based upon the recommendation of the reviewers: the protocol may be approved; approved pending clarification or incorporation of committee recommendations; deferred for major revision or clarification; or not approved. Action is based on the majority of members present at the meeting.

The CTWG's recommendations are provided to the Director for Clinical Research, and the WVU IRB. Written recommendations are given to the investigator(s). The CTWG will review deferred/disapproved protocols after modification, and if found acceptable, the approval is forwarded to the IRB for consideration.

C. Guidelines for Initiation of an Amendment

All changes in an investigator-initiated protocol are submitted to the CTRU and the CTWG in the form of an amendment and signed by the principal investigator at the time of IRB submission. Most of these are administratively reviewed. However, any major changes in the treatment intervention, increased risk, or toxicity reporting are reviewed by the full committee. All amendments are submitted to the IRB after CTWG review.

III. Investigator Initiated Protocol Development

A. Protocol Development Guidelines

A clinical trial is designed to answer a specific question or set of related scientific questions. Having a clear hypothesis and related set of scientific questions is essential to design the clinical trial appropriately and ensure that the experimental plan is well suited to address the questions.

[1]Two tips when formulating a research question and/or hypothesis:

1. It is very important that it meets the following criteria: **F**easible, **I**nteresting, **N**ovel, **E**thical and **R**elevant (**FINER**)

2. It should be as informative as possible so it should include the description of the: **P**opulation, **I**ntervention, **C**omparison group, **O**utcome (**PICO**).

[1] Guide to Clinical Research At USC: pages 50-58, October 2013

Key Steps:

- Thoroughly review internal data (i.e., laboratory and/or clinical) and perform an extensive literature review to support the hypothesis and justify the conduct of the clinical trial protocol
- Define the primary and secondary objectives, general eligibility criteria and overall experimental approach/treatment plan
- Seek statistical consultation to discuss study design (available through WVCTSI)
- Seek expert opinion on proposal
- Perform a feasibility assessment with assistance of CTRU
- Develop initial application for funding from industry sponsor (Letter of Intent) or grant Application
- Develop Initial protocol draft

[1]Protocols that are complete and descriptive facilitate the entire process of conducting clinical trials. Investigators should ensure that all essential protocol sections are completed. An important task for a coordinator is to read and re-read the protocol until it is completely clear and become as knowledgeable of every aspect of it as possible. It is a good idea to discuss all protocol specifics and who will perform the tasks involved so that there is a clear delineation of responsibilities and logistics.

The essential sections of the protocol are listed below. Note that not all studies will require all of these sections, so it is important to tailor your protocol to your individual needs and institutional/departmental requirements. Protocol templates are available from the WVCTSI and CTRU and are located in Appendix 2.

- Protocol Synopsis/summary
- Study aims/hypothesis
- Background and rationale (literature review)
- Study design
- Selection of study population and patient eligibility
- Study drug/device description
- Treatment plan
- Data management
- Data safety and management plan

B. Available WVCTSI Resources to Assist In Protocol Development

Idea Formation and Development of Mentoring Teams

WVCTSI Support: (also see Appendix 12 for contacts)

- **Hypothesis generation: Integrated Data Repository (IDR)**
  - *Biomedical Informatics Resources* Charles Mullett, *cmullett@hsc.wvu.edu*, 304-293-1017

- **Research Guidance and Mentoring Team Development**
  - *Research Pathfinder:* Julie Lockman, *jmlockman@hsc.wvu.edu*, 304-293-8044

- **Clinical Trials Working Group: Review of Concepts**
  - *Clinical Trials Research Unit:* John Naim, jnaim@hsc.wvu.edu, 304-293-4944

- **Research Concept Development Committee**
  - *Research Pathfinder:* Julie Lockman, jmlockman@hsc.wvu.edu, 304-293-8044

Study Planning and Design

WVCTSI Support: (also see Appendix 12 for contacts)

- **Evaluation of Data Availability: Integrated Data Repository (IDR): Expert Consultation**
  - *Biomedical Informatics Resources:* Charles Mullett, cmullett@hsc.wvu.edu, 304-293-1017

- **Development of Survey Instrument: RedCap**
  - *Biomedical Informatics Resources:* Charles Mullett, cmullett@hsc.wvu.edu, 304-293-1017

- **Analysis of Study Design and Data Acquisition: Research huddles, Walk-in clinics**
  - *Clinical Research Design, Epidemiology, and Biostatistics:* George Kelly, gkelley@hsc.wvu.edu, 304-293-6279

- **Research Concept Development Committee**
  - *Research Pathfinder:* Julie Lockman, jmlockman@hsc.wvu.edu, 304-293-8044

- **Clinical Trials: Assistance in planning and coordination**
  - *Clinical Trials Research Unit:* John Naim, jnaim@hsc.wvu.edu, 304-293-4944

Protocol Development

WVCTSI Support: (also see Appendix 12 for contacts)

- **Research Pathfinder Consultation**
  - *Research Pathfinder:* Julie Lockman, jmlockman@hsc.wvu.edu, 304-293-8044

- **Clinical Trials: Assistance with development of and review of Institutional Review Board (IRB) protocols**
  - *Clinical Trials Research Unit:* John Naim, jnaim@hsc.wvu.edu, 304-293-4944

- **Community-Based Participatory Research and Community-Based Trials: Guidance on IRB submission**
  - *Community Engagement and Outreach: Geri Dino, gdino@hsc.wvu.edu , 304-293-1898*

- **Research Subject Advocacy**
  - *Ethics, Regulatory Knowledge, and Support: Daniel Vasgird, daniel.vasgird@mail.wvu.edu, 304-293-6094*

- **Data Safety Monitoring and Informed Consent Process**
  - *Ethics, Regulatory Knowledge, and Support: Daniel Vasgird, daniel.vasgird@mail.wvu.edu, 304-293-6094*

- **WVU+kc system training for submission of IRB protocols**
  - *Ethics, Regulatory Knowledge, and Support: Daniel Vasgird, daniel.vasgird@mail.wvu.edu, 304-293-6094*

- **IRB protocol entry into WVU+kc**
  - *Administrative Core; Ethics, Regulatory Knowledge, and Support: Daniel Vasgird, daniel.vasgird@mail.wvu.edu, 304-293-6094*
  - *Clinical Trials Research Unit:* John Naim, *jnaim@hsc.wvu.edu, 304*-293-4944

Data Collection and Analyses

WVCTSI Support: (also see Appendix 12 for contacts)

- **Clinical Trials: Registration, consenting of patients and data acquisition**
  - *Clinical Trials Research Unit:* John Naim, *jnaim@hsc.wvu.edu,* 304-293-4944

- **Community and Practice-Based Sites: Data collection**
  - *Community Engagement and Outreach: Geri Dino, gdino@hsc.wvu.edu, 304-293-1898*

- **Data extraction/collection: Integrated Data Repository (IDR)**
  - *Biomedical Informatics Resources:* Charles Mullett, *cmullett@hsc.wvu.edu*, 304-293-1017

- **Biostatistics: Data interpretation, Statistical Power Analysis, Other stats support**
  - *Clinical Research Design, Epidemiology, and Biostatistics:* George Kelly, gkelley@hsc.wvu.edu, 304-293-6279

Research Funding

WVCTSI Support: (also see Appendix 12 for contacts)

- **Funding Opportunities**
  - *Clinical and Translational Pilot Grants Program*
    ($25,000-100,000 over a period of 18 months; varied RFA's)
  - *WVCTSI Small Grants Program*
    ($5,000 for one year, rolling submissions)

- **Grant Development and Review: Pre- and post-award services**
  - *WVCTSI Administrative Core:* Anne Bolyard, *aebolyard@hsc.wvu.edu*, 304-581-1963

Additional HSC Programs and Research Support:

West Virginia Tissue Bank—James Coad, MD, Department of Pathology
Pathology and Histology Services – Kymberly Gyure, MD
Biospecimen Processing Core—Acquiring and processing of biospecimens for use in translational cancer research—William Petros, PharmD
Bioinformatics and Biostatistics Core Facility – George Kelly, PhD
Clinical Pharmacology Shared Resource Center – William Petros, PharmD
Computation and Structure Biology Core Facility – Peter Gannet, PhD

Flow Cytometry Core Facility – Kathleen Brundage, PhD
Genomics Core Facility –Stephen DiFazio, PhD
Laboratory Animal Resources – TBN
Center for Advanced Imaging – Karyn Wallace
Microscopic Imaging Facility –Karen Martin, PhD
Animal Imaging Facility – Sarah McLaughlin
Transgenic Animal Core Facility – Peter Mathers, PhD
Molecular Medicine Core Facility – Jing Jie Yu, MD

C. Investigator Responsibilities

Investigator responsibilities are outlined herein and further described in Appendix 3. For trials governed by the FDA require investigators sign a 1572 Statement of Investigator form, complete a Supplemental Information Form and a Financial Disclosure form, and provide a copy of their current CV. By signing the 1572 Statement of Investigator form, 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.

- For pharmaceutical trials, the PI completes a 1572 Statement of Investigator form. The PI and all Co-Investigators listed on the 1572 form provide copies of their current CVs and medical licenses. All investigators listed on the 1572 form also complete a Financial Disclosure form.

- The CTRU Regulatory Office reviews all internal Financial Disclosure forms. Annually, investigators are required to complete a University Conflict of Interest (COI) form as well.

- 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.

    - They filed for either an investigational new drug application (IND) or investigational device exemption (IDE) with the FDA as applicable.

D. Human Subject Protection and GCP Training

The WVCTSI adheres to local presiding IRB guidelines for Human Subjects Protection. The WVU IRB requires certification of the PI and anyone who obtains written consent for the protocol. This requirement applies to all HSC 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.

Initial 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. 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. For a list of people that have completed the CITI Training go to:

http://orc.research.wvu.edu/human_subjects_research_and_the_irb/human_subject_training

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 HSC 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. All clinical HSC faculty and staff are required to complete GCP training and to complete a recertification every three years. Non-clinical HSC 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

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.

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.

For further guidance contact the Office of Research Integrity and Compliance (ORIC). Contact information is located within the COI website at: http://oric.research.wvu.edu/conint/coir-education-and-training

E. 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-PI or appropriately trained personnel. The PI or Co-PI 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 sign 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 addresses that the risks and benefits were addressed and the patient's level of understanding.
- 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.

HIPAA 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. The enrolling physician must sign and date the eligibility checklist. Principal Investigators co-sign (if necessary) at the earliest possible date of consent. The original signed informed consent must be provided for review and verification. After eligibility is documented, the research coordinator obtains the randomization assignment (if applicable), as specified in the study protocol. The study coordinator then will complete the registration process in the clinical trials database and protocol treatment may begin.

F. Data Safety and Monitoring Plan

All investigator-initiated protocols must have in place a Data and Safety Monitoring Plan (DSMP) approved by the HSC Clinical Trials Working Group (CTWG). 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 HSC primarily rests with the Data Safety Monitoring Board (DSMB as described in each individual protocol).

Every protocol needs a Data Safety Monitoring Plan. Data and Safety Monitoring Plans (DSMP) are meant to assure that each clinical investigation has a system for appropriate oversight and monitoring of the conduct of the clinical investigation. This oversight ensures the safety of the participants and the validity and integrity of the data. A DSMP is commensurate with the risks involved with the investigation. The DSMP can be as simple as the investigator annually submitting his/her safety and Adverse Event (AE) information to the IRB or as complex as having a Data and Safety Monitoring Board. NIH now requires a Data Safety and Monitoring Plan (DSMP) be submitted with all proposals using human subjects. Being commensurate with the risks involved all research must be categorized into four categories: Minimal Risk, Low Risk, Moderate Risk, and High Risk.

CTWG Risk Assessment for DSMP's

Minimal	Low Risk	Moderate Risk	High Risk*
• Study poses no more risk than expected in daily life (blood draw, physical exam, routine psychological testing) • Behavioral studies • Nutrition studies • Observation studies • MRI studies • Survey or Questionnaire studies	• Studies of normal volunteers using well-described research procedures (e.g. IV infusion, euglycemic clamp, indirect calorimetry, etc.) • Studies which might meet requirements for minimal review but include special populations or invasive procedures • Post marketing study Phase IV drug study or device (as defined by FDA)	• Subjects treated with placebo for a recognized disease • Involves subjects with HIV/AIDS, hepatitis, or cancer on a treatment study • Substantial risk (>5%) of a Serious Adverse Event originating from the underlying condition of the enrolled subject • Phase I or II study with available safety data in humans • Industry sponsored Phase III clinical trial$^{\perp}$	• Involves an intervention or invasive procedure with substantial risk • An investigator-initiated IND trial • Implantation of device with an IDE • Involves the use of a new chemical or drug for which there is little or no toxicology data in humans • A gene therapy study or research involving recombinant DNA molecules (gene transfer) • Investigator initiated multi-center trial$^{\perp}$ • Investigator initiated Phase III clinical trial$^{\perp}$ • Involves the manufacturing of agents on campus • Study has provisions to waive consent in emergency circumstances • Involves vulnerable populations (e.g. pediatric, pregnant, psychiatric, prisoner) • Blinded Phase I and II trials

* All high risk studies require one of the following: Independent Monitor, Safety Monitoring Committee, or Data Safety Monitoring Board (DSMB)

$^{\perp}$ Requires a DSMB

DSMP templates are found in Appendix 4.

Data Safety and Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent group of experts that advises the IRB and the study investigators. The members of the DSMB serve in an individual capacity and provide their expertise and recommendations. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to the IRB concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study. In order to determine if a DSMB is needed the research needs to be classified by risk.

Considerations for When to Create an Independent Data and Safety Monitoring Board or Committee:

- NIH Guidance:
  The NIH requires data and safety monitoring, generally, in the form of Data and Safety Monitoring Boards (DSMBs) for phase III clinical trials. For earlier trials (phase I and II), a DSMB may be appropriate if the studies have multiple clinical sites, are blinded (masked), or employ particularly high-risk interventions or vulnerable populations.
- FDA Guidance:
  DSMB's or Data Monitoring Committees (DMC) have generally been established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. DMCs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, but a DMC is not required or recommended for most clinical studies. DMCs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes. The FDA Guidance provides details on additional factors to consider when determining whether to establish a DMC for a particular trial which relate primarily to safety, practicality, and scientific validity.

If you have any further questions regarding the data safety monitoring please contact the Research Subject Advocate at researchhelp@wvu.edu or the Office of Research Integrity and Compliance at 304.293.7073.

Clinical Trials Research Unit (CTRU) Research Coordinators monitor all patients on clinical therapeutic protocols covered by the DSMP. These Coordinators evaluate patients at each treatment and follow-up encounter. Serious adverse events (SAEs) are reported to the attending physician, the principal investigator (PI), the DSMB, IRB, and to any appropriate agency. The CTRU performs data audits to ensure timely collection and accurate reporting of data. Accrual reports are run for each protocol and are provided to the CTWG and WVCTSI leadership.

Biostatistics Core Facility -This facility collects data on early stopping rules, and advises the CTWG and HSC 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 (TBE): 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 coordinators, PIs, and attending physicians involved in patient accrual. Each committee reports pertinent findings to the DSMB. SAEs are independently reported to appropriate agencies (e.g., IRB, NIH, pharmaceutical sponsor) as outlined in the DSMP.

- Phase I Patient Protocol Review Committee (TBE): 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 DSMB audits first patient entry into high-risk trials, including agents that are used first-time in humans.

- Phase II Patient Protocol Review Committee (TBE): This committee reviews all patients active on Phase II trials (quarterly) and evaluates laboratory and clinical data regarding efficacy, toxicity, response if applicable, and drug tolerance.

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

- Population Science and Bio-behavioral Research Review Committee (TBE): This group consists of members of the Population Science Research Program with expertise in population and prevention methodologies, bioethics, clinical, behavioral and preventive medicine, bio-statistics, community medicine methodologies, psychometrics and epidemiology. The committee is under the authority of the Director for Population/Community/Behavioral Health Research. 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 CTWG.

G. Serious Adverse Event Reporting

All SAEs, defined as any experience that is life threatening (grade 4) or fatal (grade 5), is permanently disabling, requires inpatient hospitalization, or identifies treatment deviation must be reported by telephone contact within 24 hours of discovery followed by a written report to the sponsoring company and IRB within 5 working days (refer to WVU IRB Policy 8.0). All SAEs must be reported to the DSMB even if in the investigator's judgment the event is not related to the investigational agent or device. The DSMB is allowed to independently review the event and to formulate its own independent attribution of the event. The table below outlines the SAE reporting procedural process and identifies responsibilities of CTRU staff.

Tabulation of Serious Adverse Events Reporting Process

SAE REPORTING ACTION ITEMS	RESPONSIBILITY
Toxicities (expected/unexpected) should be 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 (FDA, NIH, pharmaceutical company liaison) using the NIH and/or protocol guidelines.	Physician and Study Coordinator
Provide a copy of the SAE to CTRU Regulatory Office and is reported to IRB via ELECTRONIC IRB SUBMISSION SYSTEM	Study Coordinator
Log SAE into database.	Study Coordinator/Data managers

SAEs must include pertinent information and must be completed in the format defined in the protocol. This information usually includes, but is not limited to, source documents indicating the dates that each adverse event occurred, what treatment was taken, the outcomes, any follow up information and the investigator's opinion of the attribution of the event.

H. Data Acquisition

The Clinical Trials Research Unit is responsible for the registration of patients and data acquisition for all non-cancer investigator-initiated, pharmaceutical-sponsored, or multicenter national protocols. All required patient information is entered into the electronic database for all WVCTSI protocols according to the schedule outlined within each protocol. The electronic database allows remote entry from satellite or affiliate institutions, subject to review by the CTRU. For external institution 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.

I. Eligibility Verification

Prior to registration, the Research Nurse/Coordinator completes the eligibility checklist and along with supporting source documents, and signed consent, presents it to a second Research Nurse/Coordinator for verification and sign-off.

- 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.
- The original signed informed consent must be provided for review and verification.
- All eligibility source documents must be submitted with checklist.

- If either Research Nurse/Coordinator has concerns about eligibility, consent, etc., these concerns are directed to and adjudicated by Director of Clinical Research, or designated Chair DSMB, or Clinical Department Chair.

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

- Eligibility verification maybe delayed and the patient registered if study staff is not available (weekends, holidays, off-hour, etc.) or under emergency conditions. This shall be noted in patient's chart and signed by PI.

Guidelines for Eligibility Waivers for Investigator Initiated Trials

For sponsored investigator-initiated protocols, waivers may be requested.

The waiver process is as follows:

- Objective numerical data for protocol eligibility (e.g., Hgb ≥ 9.5 g/dl; creatinine ≤ 2.0 mg/dl; LVEF ≥ 40%) are not subject to wavier. In rare instances a protocol may allow variance in numerical eligibility criteria, then the procedure outlined below would apply.

- The study coordinator will present the waiver request to the PI. If the PI agrees to the waiver, he/she must provide approval in writing.

- If it is the PI is requesting the waiver, he/she must have two independent (not associated with study) physicians review and advise the DSMB (on behalf of the CTWG) on the appropriateness of the waiver.

- If the two independent reviewers agree, the waiver will be presented to the Director of the CTRU for written authorization. The protocol waiver will be accepted. If the independent reviewers disagree or the Director of the CTRU will not authorize, then the waiver is denied and there is no further recourse available.

- The research coordinator will provide a copy of the reviews and authorization to the CTRU Regulatory Office who will then advise the WVU Institutional Review Board of the waiver and obtain IRB approval.

- Second waivers **<u>are not</u>** allowed. In such cases, an amendment to the protocol should be developed.

- There will be no retroactive waivers.

Guidelines for Eligibility Waivers for Pharmaceutical and External Institutional Trials

The study coordinator will present the waiver request to the Sponsor and/or Medical Monitor of the trial. If the sponsor agrees to the waiver, the sponsor will be asked to provide written authorization documenting the eligibility override and waiver. The wavier and supporting

documents are submitted to the IRB for approval of the protocol exception. IRB approval must be obtained prior to implementing the protocol exception.

J. Budget Development

A study budget is usually developed on a per subject cost basis taking into account all personnel and procedure costs. The most efficient way to develop a budget is first produce a study schema or schedule of events that defines all study procedures and data gathering tasks for the entire study. It is suggested to use a spreadsheet format to create the budget. The spreadsheet should mirror the schedule of events for the trial. Next list all protocol procedures and tasks in one column and label each study visit across all other columns. It's important to identify standard of care (SOC) vs study related costs. That can be denoted by SOC within the spreadsheet. For sponsored protocols, a protocol and proposed budget is sent to the site. After reviewing the protocol, modify the budget to reflect the costs to conduct the trial at WVU. Appendix 5 contains a sample budget.

Cost Analysis

Start-up Costs – These are one-time costs associated with the administration of the protocol. Costs may include: Protocol development (investigator initiated), protocol review (sponsored study), IRB application preparation, regulatory document preparation, budget preparation, protocol specific training, record retention, pharmacy start-up, scientific review, IRB review, etc.

Hospital procedure/test costs are determined by West Virginia University Hospitals (WVUH). These costs are usually discounted for research and can be obtained by contacting WVUH Patient Financial Services. Labor costs for study coordination, data management, PI oversight can be calculated by using a time analysis worksheet for each study task and multiplying by an hourly rate factor. Appendix 5 contains a sample budget worksheet.

All study related procedures and tests that are paid for by the study budget must not be billed to either the subject or their insurance company. These charges must be sent to the CTRU Accounting Office for payment. This is accomplished by ordering tests and procedures using a research requisition or electronic research order set. Appendix 6 contains a protocol billing form that is used by patient financial services to set-up the electronic order set for each IRB approved protocol.

K. Trial Registration

ClinicalTrials.gov http://clinicaltrials.gov/ is a federal database for all publicly and privately supported clinical studies of human subjects conducted around the world. The FDA Amendment Act (FDAAA) of 2007 requires responsible parties in applicable clinical trials to register trials and submit summary results to ClinicalTrials.gov. In addition to the FDA, some funding agencies may require registration.

The site is a resource to patients who are seeking to participate in clinical trials, and helps ensure that null studies (studies with negative results) are published. Study subjects must be informed in the consent document that clinical trial information will be submitted to the National Institutes of Health/National Library of Medicine (NIH/NLM) for inclusion in the clinical trial registry databank.

It is the sponsor's responsibility to register clinical trials when they begin, provide timely updates, and submit summary results to clinicaltrials.gov. Sponsor-investigator trials must be registered by the Principal Investigator. The CTRU Regulatory Office may assist investigators with registering their trials.

"Applicable Clinical Trials" include:

- **Drugs and biologics trials–** clinical investigations, other than phase I clinical investigations, of drugs or biological products subject to FDA regulation

- **Device trials** – trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric post market surveillance required by FDA

L. Protocol Review and Activation

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

Investigator Initiated Protocols

- All appropriate protocol approvals and CTWG sign-offs have been completed.
- A budget has been approved either through outside support and completion of a Clinical Trials agreement or through internal HSC/WVCTSI funds approved by the HSC/WVCTSI Senior Leadership Committee.
- A budget has been approved either through outside support and completion of a Clinical Trials agreement or through internal HSC funds approved by the HSC Senior Leadership Committee.
- The protocol has been formatted per CTRU guidelines, an eligibility checklist has been developed, and data collection has been defined.
- Any required regulatory documents (for investigational drug) have been filed with the NIH and/or FDA.
- A Research Nurse or Protocol Coordinator and/or Data Manager has been assigned.
- An activation date is recorded in the electronic database.
- The activation checklist has been completed.
- Data collection has been set up in the relevant database.
- An official protocol activation notification from CTRU Administration will be sent to all clinical investigators, biostatisticians, Research Nurses/Coordinators, and Pharmacy.
- For therapeutic trials, preprinted orders have been prepared.
- Activation at collaborating institutions is determined. The CTRU administrative staff assists the PI in compliance and activation at selected collaborating institutions.

- Database Administrator registers protocol with ClinicalTrials.gov http://clinicaltrials.gov/
- Protocol specific training is provided to study team and documented and filed with protocol essential documents.

Institutional Multicenter Protocols

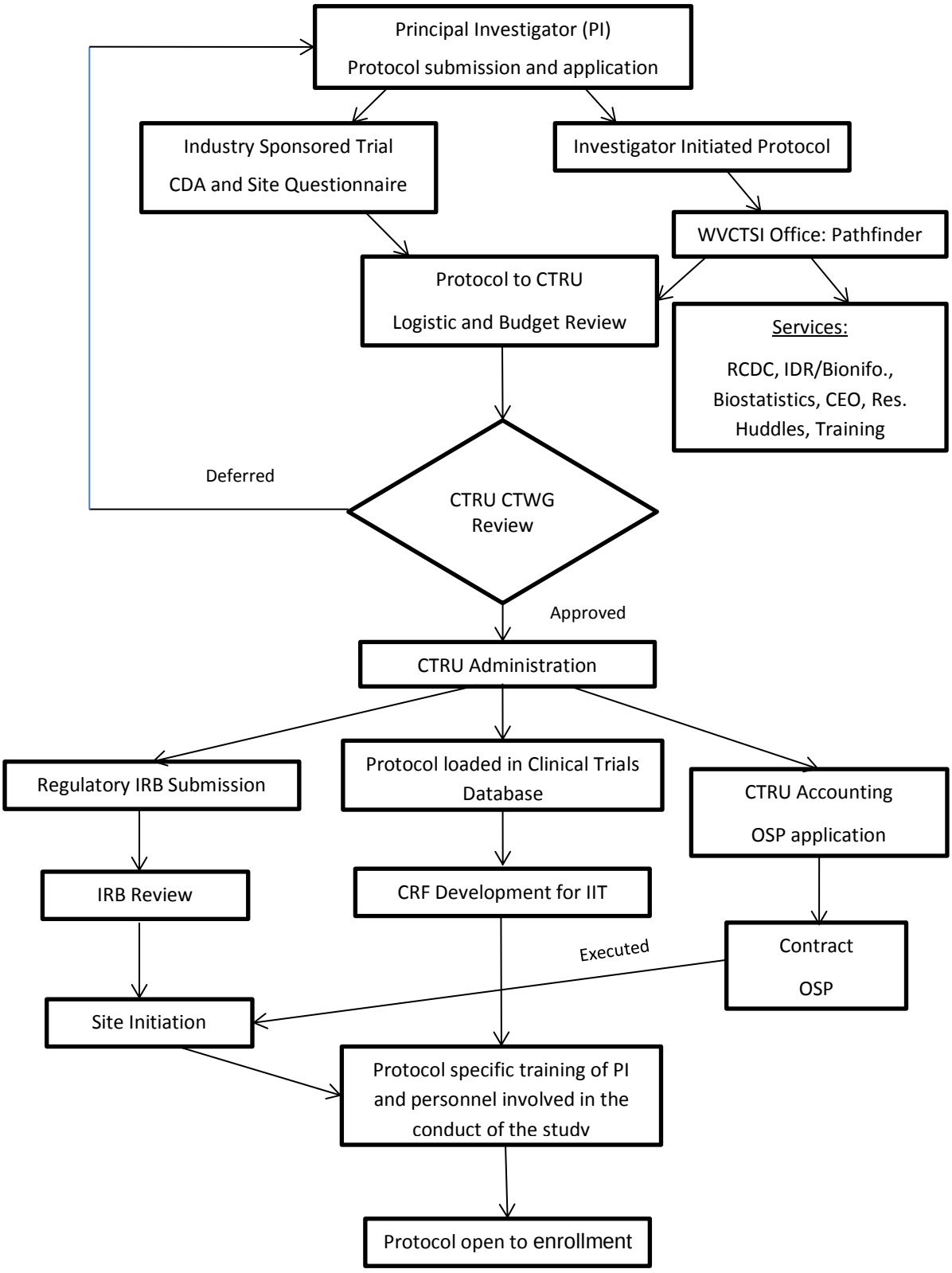
- All appropriate protocols and CTWG sign-offs have been completed.
- A Research Nurse or Protocol Coordinator and Data Manager have been assigned.
- An official protocol activation notification from CTRU Administration will be sent to all clinical investigators, biostatisticians, Research Nurse/Coordinators, and Pharmacy.
- An activation date is recorded in the electronic database.
- Protocol specific training is provided to study team and documented and filed with protocol essential documents.

Communication and Notification (TBE)

The Director for Clinical Research (for therapeutic and non-therapeutic clinical trials) sends an official notice to all HSC Clinical Departments with protocol activation. This notice provides information about the protocol objectives, targeted patient population, PI, the Research Nurse, and methods to contact them, and the prioritization of the protocol.

The protocol is then entered onto the HSC Intranet (TBE), where it becomes available to all faculty members in its full form. This electronic system maintains a listing of all HSC 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, from the electronic IRB submission system. The protocol is further disseminated via an electronic Clinical Trials Listing that serves to notify our referring physicians about protocol availability (TBE).

WVU HSC CTRU Protocol Submission and Activation Schematic



The following table outlines the protocol review and activation procedural process and identifies responsibilities of CTRU staff.

Tabulation of Protocol Review and Activation Process

ACTIVATION ACTION ITEM	RESPONSIBILITY
1. Preparation for Review	
a. Submit CTRU Application	PI
b. Place on agenda for CTWG	Chair and CTWG Coordinator
c. Assign protocol number (if applicable)	Regulatory Office
d. Collate and deliver protocols for meeting	CTWG Coordinator
2. HSC Protocol Review	
a. Scientific Review b. Scientific merit c. Prioritization for patient resources	CTWG
d. Biostatistics Review i. Measurement of effect ii. Study parameters iii. Statistical considerations	Biostatistics Core Facility via CTWG
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 vi. Budget development and negotiation	CTRU Staff Accounting Office
f. Pharmacy review i. Drug formulation/procurement ii. Medication checklist sign-off	Investigational-Pharmacy Representative
g. Prepare minutes	Chair and CTWG Coordinator
h. Distribute minutes for review to CTWG and PI, memo to PI, memo to IRB	Chair and CTWG Coordinator
i. Update electronic database	Database Administrator
3. HSC Protocol Activation	
a. Protocol activation: includes preparation and submission of regulatory documents and update of CTRU protocol files	Regulatory Office

b. Assign study coordinator	Clinical Research Manager
4. New IRB Application	
a. Abstract protocol for application for IRB	Study Coordinator, CTRU Regulatory Office
b. Obtain departmental electronic signatures	CTRU Regulatory Office
c. Deliver to WVU IRB along with copy of CTWG 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
5. Continuing Review for IRB	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
g. Submit continuing review to IRB	CTRU Regulatory Office

M. Funding Guidance

West Virginia University (WVU) now has Pivot to help you find funding opportunities, as well as possible collaborators, for your research endeavors. Login at http://pivot.cos.com to start taking advantage of all that Pivot offers to the entire WVU research community. Pivot focuses on what matters most to you—the ability to identify and connect with funding opportunities and other researchers, locally and globally. It combines the most comprehensive, editorially-maintained database of funding opportunities worth an estimated $33 billion with a unique database of 3 million scholar profiles—and growing.

N. Collaborating Institutions

Purpose

The WVCTSI coordinates investigator-initiated and other trials with selected institutions. These trials encompass institutional multicenter trials and investigator-initiated studies. The intent of establishing affiliation(s) is to enable collaboration between institutions desiring participation in unique studies that would otherwise be unavailable to them and to enhance patient participation and clinical trials access to state-of-the-art therapies for residents of West Virginia. 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 HSC Clinical Departments to achieve protocol objectives in a timely manner. As the coordinating center, the WVCTSI maintains the highest possible standards through oversight of data including toxicity and response, and strict adherence to Good Clinical Practice (GCP) guidance.

Criteria for Selection of Collaborating Institutions

For investigator-initiated studies, institutions are selected at the discretion of the WVCTSI 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.

Activation Policy at Collaborating Institutions

Participation in a WVCTSI trial by an investigator from a collaborating institution is approved when all of the following have occurred:

Each institution has submitted the following prior to activation:

1. Institutional Assurance of Compliance.

2. The current Office for Human Research Protection (OHRP) assurance number and effective date(s).

3. Laboratory compliance materials: Copy of CLIA laboratory certificate of compliance from the Department of Health and Human Services Health Care Financing Administration; copy of the College of American Pathologists certificate (CAP); and a copy of the normal range of laboratory values with corresponding units. These materials are required of every laboratory used in the conduct of the study, and should be listed on the Form 1572.

4. A copy of the current IRB approval.

5. A copy of the approved informed consent document.

   The CTRU provides each institution with a sample consent that has been approved by the sponsor and is to be used as a model for each protocol. In order to assure sponsor compliance, each consent form from the collaborating site will be reviewed and

approved by HSC PI or designee prior to activation. The PI of the HSC resolves any discrepancies.

The consent must include:

- A statement that the study involves research,
- The purpose of the study,
- A description of the procedures and/or treatment,
- The procedures to be performed to monitor the patients,
- The potential risks/discomforts,
- The possible benefits,
- Possible alternatives,
- A confidentiality statement, which includes oversight by state and federal authorities as well as the HSC designated study staff.
- A statement addressing compensation for study-related injury,
- A statement that emergency treatment or injury will or will not be provided,
- A contact person for research questions,
- A voluntary participation statement, and
- A cost statement.

6. Proof of Human Subject Protection education for each participating investigator.

7. Clinician Requirements – each PI of the collaborating site will provide:

    1. Form FDA 1572 - This is the statement of investigator, which summarizes what the FDA requires for an acceptable clinical study. It must be signed and dated by the PI. In addition, all sub-investigators (if any) who are participating in the study must be listed on the PI's Form 1572. The investigational pharmacist and all sites (including laboratories) being used in the study must also be listed. Each investigator participating in drug or biologic studies is required to have a Form 1572 on file with the FDA. It is the responsibility of the collaborating PI to ensure that the sub-investigators have the Form 1572 on file.

    2. Curriculum Vitae (CV). The front page must be signed and dated – CVs are considered current for one year.

Once the collaborating institution's IRB approval, consent approval, and regulatory data have been reviewed and accepted, the collaborating institution's PI is notified in writing that the protocol is open for accrual at his/her site. At that time, protocol-specific case report forms (CRFs) are faxed or mailed to the site, and a site initiation telephone call is conducted. This call includes the HSC PI and Network Coordinator (TBN) and/or Research Nurse/Coordinator from the HSC, together with the research staff from the collaborating site. All questions can be answered, and data expectations are reviewed. The site will receive written instructions as to data expectations and study conduct; phone/fax numbers of the HSC research staff are also provided. The HSC Network Coordinator acts as a liaison to facilitate regulatory and protocol compliance throughout the conduct of the study.

Study Conduct Expectations at Collaborating Sites

To ensure quality performance, each collaborating site PI receives must follow the conduct expectations described below.

Data Submission

In order to ensure protocol adherence, all eligibility documents (consent, eligibility checklist, and source documents) are presented to the Network Coordinator (TBN) prior to randomization/registration. Written confirmation will be sent to the site once the patient has been enrolled in to the study to verify the unique patient identifier and the dose/level/cohort as applicable.

General Conduct of the Study

HSC Instructions for Collaborating Institutions outlines the specific clinical practices to be adhered to at each site. The Network Coordinator will provide copies of all Serious Adverse Events (SAEs) and safety notices reported by all sources to each site. The respective Institutional Review Boards (IRB) of each collaborating site should review all reports. The HSC PI will determine how the study communication between sites is to be provided. This most often is in the form of monthly phone conferences. All reported adverse events are reconciled with the toxicity report forms, and a summary of specimen collection is reviewed. Minutes of the calls are distributed to all participating sites, and are periodically reviewed by the PRMC.

Toxicity and Response Reporting Requirements

HSC Instructions for Collaborating Institutions details the toxicity and expedited reporting guidelines. In order to maintain uniformity, it is the responsibility of the HSC DSMB to review all responses. Confirmation of responses is conveyed in writing to the collaborating member. Adherence to the regulations for data, toxicity and response reporting, and maintenance of GCPs ensure the quality and integrity of the trials.

IV. Industry Sponsored Protocols

A. Confidentiality Disclosure Agreement

Investigators bring Confidentiality Disclosure Agreements (CDAs) from pharmaceutical sponsors to the Director CTRU for institutional routing and signature by the WVU Office of Technology Transfer. Technology Transfer signs and submits the CDA to the pharmaceutical sponsor. CTRU then receives a copy of the protocol to proceed with feasibility and assessment for participation.

B. Feasibility Assessment

Before a sponsor will select a site to conduct the study, they will usually have the site complete a feasibility questionnaire. This tool will assist the sponsor with determining if the site is qualified to conduct the trial, so it's important to answer their questions as accurately as possible. The

questionnaire will generally ask for the full name of the institution, names and contact information of the PI, study coordinator, budget and contract coordinator, etc. The sponsor will ask specific information about the patient population at the site, number patients seen by the PI, estimated number of subjects the site may accrue in a specific time period (weekly, monthly or yearly), number of similar trials the PI has participated in the past, number of trials the study coordinator has been assigned, access to refrigerators/freezers, dry ice, IRB information, etc. The WVCTSI Bioinformatics (BMIR) group can assist with estimating the number of potential subjects available.

In addition to the sponsor's assessment, the site should perform its own internal assessment. This should be performed soon after the complete protocol is available. It's important to involve the study team with the assessment. A study coordinator assessment tool is located in Appendix 7.

C. Budget Review and Cost Analysis

For sponsored protocols a proposed budget is sent to the site usually soon after site selection. After reviewing the protocol, modify the budget to reflect the costs to conduct the trial at WVU. It's important to identify standard of care (SOC) vs study related costs. The study coordinator and PI should thoroughly review the protocol and determine all study related procedures/tests vs standard of care (SOC). The sponsor is responsible for all study related procedure costs. All study related charges should be billed to a research account.

V. Core Descriptions and Processes

A. Bioinformatics and Biostatistics Core Facility

This core provides biostatistical and epidemiological consulting services to researchers in the HSC at WVU. Services include study design, power analysis, data analysis and interpretation, and assistance with reporting of results. 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.

Contact	Phone	Email	Website
George Kelly, Ph.D.	304-293-6279	gkelley@hsc.wvu.edu	http://www.hsc.wvu.edu/bcg

B. Biospecimen Processing Core

The Biospecimen Processing Core (BPC) provides services to members and other research labs by acquiring and processing accurately timed, high quality samples (e.g., blood, urine, bone marrow, etc., but excluding tissue) from patients for translational research. The sample processing complexity is determined by needs of the investigators and ranges from simple logging and storage to generation of specific subsamples.

Functions of the BPC include: assistance with protocol design of sample times; establishment of handling procedures; determination of sample stability; sample & data acquisition from clinics and

Ruby/WVU Hospital; serving as an interface between the clinicians and labs; and specimen stabilization/processing, storage/shipping.

Contact	Phone	Email	Website
William Petros, PharmD	304-293-0495	wpetros@hsc.wvu.edu	http://wvucancer.org/Cores/BioSpecimen-Process

C. Clinical Trials Research Unit

The Clinical Trials Research Unit (CTRU) core facility is dedicated to providing services and expertise to the faculty and staff of the WVU HSC to support the clinical research enterprise.

Services include:

- Contract and budget preparation protocol review and feasibility assessment, IRB application preparation and submission, filing of all regulatory documents and financial monitoring.
- Clinical services by qualified research coordinators include: training of staff, study coordination, case report management, source documentation, test article inventory and accountability, adverse event reporting, and study close out.
- Data management includes creating data collection forms and maintaining study and CTRU databases.

Contact	Phone	Email	Website
John Naim, Ph.D.	304-293-4944	jnaim@hsc.wvu.edu	http://wvucancer.org/ctru

D. Clinical Pharmacology Shared Resource Core Facility

This Core provides assistance with the design, implementation, bio analytical and data analysis for studies involving the clinical pharmacology of pharmaceutical agents. Services include complete LC-MS-MS determination of drug concentrations in biologic samples as well as pharmacokinetic-pharmacodynamics modeling.

Contact	Phone	Email	Website
William Petros, PharmD	304-293-0495	wpetros@hsc.wvu.edu	http://www.wvucancer.org/Cores/Clinical-Pharmacology-Share

E. Genomics Core Facility

Our goal is to provide comprehensive services in microarray, DNA sequencing including Next Generation Sequencing, and bioinformatics for investigators who are conducting basic, clinical and translational biomedical research. To most effectively provide these services, we are partnering with WVU Cancer Center Bioinformatics Core, and West Virginia INBRE Program Bioinformatics Core.

The WVU Genomics Core is supported by WVU Center of Neuroscience COBRE (Centers of Biomedical Research Excellence, NCRR), West Virginia Clinical Translational Science Institute (WVCTSI), Health Science Center (HSC), and WV-INBRE.

Services include: Affymetrix Microarray; Agilent Microarray; DNA Sequencing; Next Generation Sequencing

Contact	Phone	Email	Website
Stephen DiFazio, Ph.D.	304-293-5314	Stephen.difazio@mail.wvu.edu	http://biology.wvu.edu/facilities/genomics_core

F. Molecular Medicine Core Facility

The Molecular Medicine Core (MMC) at the WVU Health Sciences Center offers a broad range of laboratory services in gene-based molecular medicine, as well as training and consultation.

The Molecular Medicine Core offers a full-service gene analysis program -- including project, assay and primer design -- and experiments relating to genotyping analysis and gene expression assays. MMC services include sample preparation (fresh & paraffin-imbedded tissues, blood, and all other types), DNA/RNA extraction, reverse transcription-polymerase chain reaction (RT-PCR), products purification, DNA sequencing, SNP, and pathogen detection for clinical research. The following techniques are utilized: RT-PCR, Real-Time Quantitative PCR with SYBR green dye or with TaqMan probe chemistry, CEQ SNP Primer Extension, TaqMan Allele Discrimination, and direct DNA sequencing. The Molecular Medicine Core houses state-of-the-art specialized equipment, including ABI 7500 Fast Real Time PCR System, CEQ 8000 Genetic Analysis System, ABI Prism DNA Sequencer, ABI Thermal Cyclers, and other equipment required for gene amplification, DNA sequencing, SNP, and pathogen detection.

The MMC staff routinely use two different DNA sequencing systems to double-check findings, which enables the Core to provide high quality and highly reliable services. In addition, the Core is continually developing novel techniques and assays for more effective detection of DNA variation and gene expression. The Core provides timely reporting of all results and methodologies, with full interpretation of data and follow-up consultation as needed.

Contact	Phone	Email	Website
Jing Jie Yu, MD	304-293-8661	jyu@hsc.wvu.edu	http://wvucancer.org/mmc/Home

G. Pathology and Histology Services

The Anatomic Pathology Division of the Pathology Department offers various services, including the Autopsy Service, Surgical Pathology, Cytopathology and Neuropathology analysis. This group has a collection of paraffin embedded tissues that can be accessed for immunohistochemical analysis. A centralized Histology Laboratory, which provides routine processing, sectioning and staining of body tissues, as well as a wide variety of special stains and advanced immunohistochemical procedures are

available on a charge basis. On-site technicians will section requested tissues and perform immunohistochemical labeling on a charge basis. Optionally, sections can be mounted on slides and the investigator may process immunohistochemical labeling. This section prepares 250,000 slides a year for pathologic examination. In the Cytopathology Laboratory, cellular morphology studies are performed on a variety of specimens, including gynecologic smears, body fluids and fine needle aspirations. The Cytopathology Laboratory examines 8,000 gynecologic specimens and 2,500 non-gynecologic specimens annually. About 300 fine needle aspirations are performed each year.

It is the goal of the Pathology Laboratory for Translational Medicine to provide the research community with the technical services necessary for growth and development in the world of investigative research. The services that will be provided by the laboratory are essential to an institution upholding a status of high recognition nationally and internationally. At a time when new discoveries generated by basic biomedical research are applied to pathology practice, accessibility to the most modern scientific methods becomes imperative.

Contact	Phone	Email	Website
Kymberly Gyure, M.D.	304-293-1625	kgyure@hsc.wvu.edu	http://www.hsc.wvu.edu/som/Pathology/Research/Tissue-Bank/Laboratory-Services.aspx

H. Electron Microscopy Core Facility

A Health Sciences Center (HSC) Core Electron Microscopy Facility provides complete scanning and transmission EM services on a fee-for-use basis. This well-equipped center is staffed full-time and supervised by faculty from the Departments of Pathology and Anatomy. Investigators can obtain consultation regarding experimental design, as well as expert tissue preparation and ultra-thin sectioning services. One of the two microscopes is a recently purchased JEOL TEM, and both instruments are covered by the manufacturer's service contracts.

The Core EM facility also offers complete darkroom services. The HSC Microscope Imaging Facility offers a comprehensive confocal imaging system (Zeiss LSM-510) and an integrated microscopy system for neuroanatomical 3-D reconstruction and design-based stereology (Neurolucida and Stereo Investigator; MicroBrightfield, Inc.).

Contact	Phone	Email	Website
Karen H. Martin, Ph.D.	304-293-6965	kmartin@hsc.wvu.edu	http://anatomy.hsc.wvu.edu/mif/

I. Center for Advanced Imaging

The Center for Advanced Imaging is operated by the WVU Department of Radiology The PET/CT facility uses a Siemens Medical Systems Biograph 16 PET/CT scanner and a Philips Medical Systems Gemini time-of-flight PET/CT scanner. Both systems are capable of quantitative whole body clinical imaging.

In addition, The Center for Advanced Imaging houses a General Electric Medical Systems PETtrace cyclotron capable of producing the most common PET radionuclides (11C, 18F, 13N and 15O). This facility also has the equipment for synthesis of a number of PET radiopharmaceuticals. The MRI facility operates five MRI scanners: a Siemens Medical Systems Vario 3T scanner, two Siemens Medical Systems 1.5T Avanto scanners, a General Electric Medical Systems 1.5T Twin Speed scanner and a Philip Medical Systems 1T Panorama open MRI scanner. All the systems have clinical imaging capabilities.

The outstanding imaging facilities and staff at the CAI form the clinical arm of the Center. An image-focused NIH-funded group of laboratories form the other research arm.

Contact	Phone	Email	Website
Raymond Raylman, PhD	304-293-1973	rraylman@hsc.wvu.edu	http://medicine.hsc.wvu.edu/radio/Research/Research

J. Flow Cytometry Core Facility

The Flow Cytometry Core Facility provides instrumentation and scientific support for cell analysis and cell sorting on a fee basis. The facility is equipped with two cytometers a Becton-Dickenson FACSCalibur and a FACSAria along with a Miltenyi Biotec AutoMACS magnetic bead cell sorting system. The FACSAria is a 15 parameter high speed bench top sorter capable of sorting cells into 4 separate populations. It has the capacity to sort into tubes or tissue culture plates and has both an aerosol management system for aseptic sorting and a temperature control option for maintaining the temperature of sorted samples. The FACSCalibur is equipped with an autoloader and has the capability of 4 color analysis.

The Flow Cytometry Core has several software packages including CellQuest Pro, ModfitLT and BD Diva software for data acquisition and analysis. Services provided by this facility include analysis of cell surface phenotype, intracellular protein expression, cell cycle analysis, cytokine production, and cell sorting of eukaryotic cells. In addition, phenotypic analysis, quantitation and sorting of prokaryotic cells is available. In addition, Core staff is available for consultations on experimental design and data analysis.

Contact	Phone	Email	Website
Kathleen Brundage, Ph.D.	304-293-6273	flowcore@hsc.wvu.edu	http://www.hsc.wvu.edu/ResOff/Pages/Research/Shared-Research-Resources/Flow-Cytometry-Core-Facility

K. Tissue Bank and Research Laboratory

Tissue-based research is increasingly contributing to the understanding of human disease, especially in genomics and proteomics based research. Tissue Banks make it possible to use human tissue in research. The West Virginia University Tissue Bank collects a wide variety of normal and diseased tissue from surgical resections and autopsies with Institutional Review Board approval and patient consent. Specimens are given to researchers without any patient identifying information. However, researchers may need to know basic demographic information which is collected and then

deidentified (i.e.identifying information is removed) at the time of tissue banking. Approval from the Institutional Review Board and the Tissue Bank Board of Directors are required for all projects utilizing these tissues.

Skilled technologists work with surgeons, pathologists, and researchers to maximize the scientific value and quality of acquired tissue. They oversee designation of tissue so investigators can correlate pathologic features with their data while maintaining patient confidentiality. Tissues are obtained fresh, frozen in liquid nitrogen, embedded in the cryopreservative O.C.T., and/or fixed in formalin and paraffin embedded. Histology services are also available. The WVU Tissue Bank operates with a research facility to provide slides, stains or other technical assistance to the research community.

Contact	**Phone**	**Email**	**Website**
James Coad, M.D.	304-293-1614	jcoad@hsc.wvu.edu	http://www.hsc.wvu.edu/som/Pathology/Research/Tissue-Bank/Default.aspx

Appendices

Appendix 1 – Clinical Trials Working Group Members

Member Name	Department (School)	Email
Anne Bolyard, EdD, CRA, CPRA	WV Clinical & Translational Science Institute	aebolyard@hsc.wvu.edu
Paul Chantler, PhD	Human Performance - Exercise Physiology (SOM)	pchantler@hsc.wvu.edu
Susan Collins, MS, RN	Clinical Trials Research Unit (HSC)	scollins@hsc.wvu.edu
Geri Dino, PhD	WV Prevention Research Center (SPH)	gdino@hsc.wvu.edu
Mary Fanning, DNP, RN, NEA-BC	WVU Medicine (WVUM)	fanningm@wvumedicine.com
Judith Feinberg, MD	Behavioral Medicine & Psychiatry (SOM)	judith.feinberg@hsc.wvu.edu
Richard Gross, PhD	Behavioral Medicine & Psychiatry (SOM)	rgross@hsc.wvu.edu
Sally Hodder, MD	WV Clinical & Translational Science Institute	slhodder@hsc.wvu.edu
Kim Innes, PhD	Epidemiology (SPH)	kinnes@hsc.wvu.edu
Dana King, MD, MS	Family Medicine	kingdana@wvumedicine.org
Julie Lockman, PhD	WV Clinical & Translational Science Institute	jmlockman@hsc.wvu.edu
Suresh Madhavan, PhD	Pharmaceutical Systems & Policy (SOP)	smadhavan@hsc.wvu.edu
Gina Maiocco, PhD, RN	School of Nursing (SON)	gmaiocco@hsc.wvu.edu
John Naim, PhD (Chair)	Clinical Trials Research Unit	jnaim@hsc.wvu.edu
William Petros, PharmD	Basic Pharmaceutical Sciences (SOP)	wpetros@hsc.wvu.edu
Mark Polak, MD	Pediatrics (SOM)	mpolak@hsc.wvu.edu
Rebecca Schmidt, DO, FACP	Nephrology (SOM)	rschmidt@hsc.wvu.edu
Sijin Wen, PhD	Biostatistics (SPH)	siwen@hsc.wvu.edu

Appendix 2 - Protocol Templates

Interventional Research Protocol Template - (Double click on the page to open the full document)

TABLE OF CONTENTS

Study Protocol Template

Instructions:

This protocol template is a tool to facilitate the development of a study protocol specifically designed for the investigator initiated studies. It contains sample text to assist investigators in answering the questions reviewers may have. Protocol template instructions and samples are in *italics.* Please delete the italicized text and the instructions after you complete each section.

It is recommended that section headings in the protocol template should not be deleted. It facilitates the review process. If the heading does not relate to your study insert N/A. Start from here:

Study Protocol Title:

Be consistent with the Title throughout your application, protocol and the regulatory documents

Table of Contents:

List of Abbreviations:

Use commonly used abbreviations and acronym.

Principal Investigator, Research Team, and Study Site:

Principal investigator: Co-

Investigators:

Research team and contact Information:

Study site:

Research Synopsis

Study Title

Enter the full title

Study Population

Include a brief description of the population such as health status, gender, age, etc.

Study Design

Appendix 3 – Investigator Responsibilities

(Control + click to open the full document)

http://www.fda.gov/downloads/Drugs/.../Guidances/UCM187772.pdf

Appendix 4 – Data and Safety Monitoring Plan

Data and Safety Monitoring Plan for Moderate to High Risk Studies

Study Title: [insert]

Principal Investigator: [insert name, title(s)]

Brief Study Overview

[Insert a brief description/abstract of the study here]

Oversight Responsibilities

Day-to-day oversight of the trial is [provided by the Principal Investigator (PI), [insert PI's full name]. Along with [insert names of additional investigators who will be actively involved in the conduct of the study], [insert PI's name] assures that an IRB approved informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB approved research plan. [Insert PI's name plus co-investigator names] review all study data and adverse events (AEs) real-time, and report all AE's to the [insert as appropriate: DSMB, Data Monitoring Committee (DMC) chair, sponsor] and IRB according to the IRB approved DSMP.

Monitor

Monitoring for the study is provided by [insert name of the organization, if applicable], including regular data monitoring at the site and regular review by [insert as appropriate: DMC, NIH DMSB, sponsor investigator].

Monitoring Procedures

The [insert monitoring body, for example: medical monitor, DMSB] reviews study conduct [specify what will be included in reports to the monitoring body: accrual, drop-outs, protocol deviations] and AEs in aggregate on a [provide a time interval, for example: weekly, monthly, quarterly, semi-annual, annual] basis. The [insert monitoring body listed above] reviews serious adverse events (SAEs), [if applicable: dose limiting toxicities], and [list other specific intervention complications] in real-time. [If applicable, add any other additional reviews the monitoring body will do].

Study data are provided to the [insert monitoring body listed above] prior to each [insert time interval listed above] review [and if applicable, describe additional monitoring planned]. Data reports are prepared by the [insert party responsible for putting together these reports, for example: study statistician].

Monitoring Report

The [insert monitoring body listed above] provides a written report to the study team with recommendations for study modification, study continuation/discontinuation as relevant.

The study team is responsible for forwarding the report to the IRB.

Collection and Reporting of SAEs and AEs

For this study, the following standard AE definitions are used:

> **Adverse event:** Any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.
>
> **Serious Adverse Event:** Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

AEs are graded according to the following scale [use scale below or whatever scale is proposed for the study]:

> **Mild:** An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
>
> **Moderate:** An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.
>
> **Severe:** An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale [use scale below or whatever scale is proposed for the study]:

> **Not Related:** The AE is clearly not related to the study procedures 9i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
>
> **Possibly related:** An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
>
> **Related:** The AE is clearly related to the study procedures.

AEs are identified [describe how AEs will be captured, for example: during hospital admission when potential AEs are assessed through a review of the hospital chart on a daily basis and a physical examination of the subject. After discharge, AEs are assessed at time of study follow-up visits].

SAEs and specific procedure-associated AEs are reported to the [insert monitoring body listed above] within 24 hours. In addition, all AEs are reported according to the [insert name of the IRB overseeing the study] AE reporting guidelines.

Management of Risks to Subjects

Expected AEs

Expected AEs associated with the [insert: drugs being used in the study and study procedures] include:

- [List expected toxicities of the study drugs/procedures].

AE Management

[If applicable, insert description of any specific management plans for expected AEs].

Dose Escalation and Dose-Limiting Toxicities

[If applicable, insert description of plan for dose escalation and what will be considered dose-limiting toxicities].

Data Analysis Plans

[Describe the planned interim analysis for efficacy, safety, or both. Specify the safety parameters that will be reviewed (for example: expected AEs in aggregate, all SAEs, and dose-limiting toxicities]

Plan for Data Management

The [insert data monitoring body listed under "Monitoring" above] reviews study data on a [provide time interval: monthly, quarterly, semi-annual, annual] basis. [If applicable: In addition, a site monitor does an initial site visit for training and a close out visit at the end of the study. The site monitor reviews all regulatory documents for compliance and study documents for data accuracy and completeness].

Confidentiality throughout the trial is maintained by [insert description of study-specific confidentiality procedures].

Data Safety and Monitoring Plan for Low-Risk Studies

Study Title: [Insert]

Brief Study Overview

[Insert a brief description/abstract of the study here.]

Oversight Responsibilities

Oversight of the trial is provided by the [Principal Investigator (PI), Dr. [Insert Pi last name] and [insert names of additional investigators (co-investigators) who will be actively involved in the conduct of the study].

Monitoring Procedures

Dr. [insert PI last name] assures that IRB approved informed consent is obtained prior to performing any research procedures, that all subjects meet eligibility criteria, and that the study is conducted according to the IRB-approved research plan.

Study data are accessible at all times for the PI [insert if applicable: and co-investigators] to review. The PI [insert if applicable: and co-investigators] review(s) study conduct ([specify what will be reviewed: accrual, drop-outs, protocol deviations) on a [provide time interval, for example: weekly, monthly, quarterly, semi-annual, annual] basis. The PI [insert if applicable: and co-investigators] review(s) AEs individually real-time and in aggregate on a [provide time interval, for example: weekly, monthly, quarterly, semi-annual, annual] basis. The PI [insert if applicable: and co-investigators] review(s) serious adverse events (SAEs), [if applicable: dose limiting toxicities] and [list all other specific intervention complications] in real-time. [If applicable, add any other additional reviews the PI/co-investigators will do]. The PI ensures all protocol deviations, AEs , and SAEs are reported to the [if applicable: sponsor] and IRB according to the applicable regulatory requirements.

Collection and Reporting of SAEs and AEs

For this study, the following standard AE definitions are used:

> **Adverse event:** Any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.
>
> **Serious Adverse Event:** Any AE that results in any of the following outcomes:

- Death
- Life-threatening
- Event requiring inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

AEs are graded according to the following scale [use scale below or whatever scale is proposed for the study]:

> **Mild:** An experience that is transient, and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. This includes transient laboratory test alterations.
>
> **Moderate:** An experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.
>
> **Severe:** An experience that requires therapeutic intervention. The experience interrupts usual daily activities. If hospitalization (or prolongation of hospitalization) is required for treatment it becomes an SAE.

The study uses the following AE attribution scale [use scale below or whatever scale is proposed for the study]:

> **Not Related:** The AE is clearly not related to the study procedures 9i.e., another cause of the event is most plausible and/or a clinically plausible temporal sequence is inconsistent with the onset of the event).
>
> **Possibly related:** An event that follows a reasonable temporal sequence from the initiation of study procedures, but that could readily have been produced by a number of other factors.
>
> **Related:** The AE is clearly related to the study procedures.

AEs are identified [describe how AEs will be captured, for example: during hospital admission when potential AEs are assessed through a review of the hospital chart on a daily basis and a physical examination of the subject. After discharge, AEs are assessed at time of study follow-up visits].

SAEs and specific procedure-associated AEs are reported to the [insert monitoring body listed above] within 24 hours. In addition, all AEs are reported according to the [insert name of the IRB overseeing the study] AE reporting guidelines.

Management of Risks to Subjects

<u>Expected AEs</u>

Expected AEs associated with the [insert: drugs being used in the study and study procedures] include:

- [List expected toxicities of the study drugs/procedures].

AE Management

[If applicable, insert description of any specific management plans for expected AEs].

Dose Escalation and Dose-Limiting Toxicities

[If applicable, insert description of plan for dose escalation and what will be considered dose-limiting toxicities].

Data Analysis Plans

[Describe the planned interim analysis for efficacy, safety, or both. Specify the safety parameters that will be reviewed (for example: expected AEs in aggregate, all SAEs, and dose-limiting toxicities] Describe study stopping rules, if applicable.

Plan for Data Management

The [insert data monitoring body listed under "Monitoring" above] reviews study data on a [provide time interval: monthly, quarterly, semi-annual, annual] basis. [If applicable: In addition, a site monitor does an initial site visit for training and a close out visit at the end of the study. The site monitor reviews all regulatory documents for compliance and study documents for data accuracy and completeness].

Confidentiality throughout the trial is maintained by [insert description of study-specific confidentiality procedures].

Appendix 5 – Sample Budget and Worksheet

DRAFT BUDGET: 04/17/08	**Site: West Virginia University**									**Sponsor:**							
Principal Investigator:				**Study Coordinator:**								Shipping Address for CRF:					
Sub-Investigator(s)												Shipping Address for Drug:					
Title:																	
Per Patient Itemized List of Costs																	
ITEM	Visit #1 Pre-op Consent, Surgery & MRI	Visit # 2 Post-op MRI	Visit # 3 Pre-Leukapheresis & Study Consent	Visit # 4 Leukapheresis	Visit # 5 Baseline	Enrollment	Visit # 6 Time 0 Injection 1	Visit # 9 month 2 Injection 4	Visit # 10 month 4 Injection 5	Visit #11 month 6	Visit # 12 month 8 Injection 6	Visit #13 month 10	Visit # 14 month 12 Injection 7	Total per Patient			
PERSONNEL COSTS:																	
P.I.*	$150		$150	$500	$150		$125	$125	$125	$75	$125	$75	$125	$1,725			
Local Pathology	SOC													$0			
Local Pathology Tumor Processing			$300											$300			
Study RN/ Data Management	$200		$200		$200		$200	$200	$200	$150	$200	$150	$200	$1,900			
Tumor Collection	$50													$50			
PHARMACY COSTS																	
Dose Preparation							$150	$150	$150		$150		$150	$750			
IMAGING:																	
MRI w/wo contrast	SOC	SOC	SOC		SOC			SOC	SOC	SOC	SOC	SOC	SOC	$0			
LEUKAPHERESIS:																	
Pheresis lab charge				$2,500										$2,500			
LABORATORY:																	
Infectious Disease Testing		$100												$100			
Phlebotomy (for central lab)**			$25		$25		$25	$25	$25	$25	$25	$25	$25	$225			
Total Direct per patient	$400	$100	$675	$3,000	$375	$0	$500	$500	$500	$250	$500	$250	$500	$7,550			
Total Indirect Costs/patient	$104	$26	$176	$780	$98	$0	$130	$130	$130	$65	$130	$65	$130	$1,963	26.0%	Indirect Costs	
Total (Direct + Indirect Costs)/patient	$504	$126	$851	$3,780	$473	$0	$630	$630	$630	$315	$630	$315	$630	**$9,513**			

		Direct	Indirect	
	Total Patients			32.00
	Total per Patient	$7,550.00	$1,963.00	$9,513
	Total			**$304,416**

*Fee includes non-standard of care, trial specific visit procedures

**Since multiple tests are being performed, only one venipuncture fee applies.

SOC =STANDARD OF CARE

Study Budget Worksheet

Protocol Title:

Budget Item	Repeated	Research Nurse/Coord	Data Manager	PI	Reg. Assoc.	Acct.	Total
Start-up							
Protocol feasibility meeting							
Feasibility questionnaire							
Site Qualification Visit (telephone)							
Site initiation visit							
OnCore Database set up							
Conduct Staff In-services							
Preparation of regulatory documents							
Prepare IRB application and submission							
Prepare, distribute, and collect financial disclosure documents							
Budget review and preparation							
Account set-up							
Organize and receipt of study supplies							
Per Subject (screening)							
Weekly screening log faxed							
Weekly phone call to review screening activities							
Consent subjects/each							
Medical history review							
inclusion/exclusion review							
Con. Meds							
Requires central lab submission							
Requires tissue submission							
IVRS registration							
Review eligibility							

Per Subject (treatment visit)							
Schedule subjects / each							
Oversee Administration of trial medications /each							
Review and record AEs							
Con. Meds							
Schedule return visits							
Complete source documents							
CRF completion							
Resolve Data Queries							
Radiology review, tumor measurements							
Central lab collection and shipment							
Pharmacokinetics specimen collection							
Coordinate/Attend Monitoring Visits							
Preparation enrollment log							
Coordinate/Attend Study Termination Visit							
IRB Correspondence							
Protocol Amendments							
Sponsor Correspondence							
Collect/Update/Maintain Regulatory Documents							
Other							

Appendix 6 – Billing Order Set

Department Study Coordinators must complete and submit the following information to the WVUH & UHA billing departments via the "Research Billing" email distribution group in Outlook prior to the study or trial start date.

IRB #	
Trial or Study Name	
Principal Investigator	
Coordinator Name	
Coordinator Phone Number	
Inpatient, Outpatient, or both	
Study End Date	
List of Study-related Tests and/or Procedures and/or CPT codes	

Appendix 7 – Study Coordinator Assessment Tool

Clinical Trials Research Unit (CTRU)

Study Coordinator Evaluation Form for the CTWG

Full protocol title:

Protocol Number: _____

Review the protocol and complete the items below.

Circle answer and comment as applicable.

Eligibility				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 Clinical 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: _____

_____

_____

_____

Study Coordinator: _____ Date: _____

Appendix 8 – CTRU Application

Clinical Trials Research Unit
Service Application

Please attach *complete protocol to this application and submit to John Naim, PhD, Director CTRU at jnaim@hsc.wvu.edu or PO Box 9260

*Complete protocol should contain sufficient detail to allow for scientific and feasibility evaluation. Sections to include: introduction, rationale/hypothesis, eligibility criteria (inclusion/exclusion), randomization/registration procedures, treatment plan or study design, outcome measures, statistical considerations, patient consent and references.

Protocol Information

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

Study Type:

- ❑ Industry Sponsored
- ❑ Investigator Initiated (Please include biosketch)
- ❑ Multi-Site Institutional Non-profit Sponsored

Other (Describe) _____

Study Duration: Projected Start Date_____
Close Date_____

Accrual Goal: _____

Services Available (check all that apply)

□ Study Coordination □ IRB application preparation □ Data collection □ Specimen collection

□ CRF development □ Budget preparation and accounting □ Other_____

Your request for services will be evaluated by the CTRU Clinical Trials Working Group. Resource allocation decisions are focused on the potential for attracting future extramural funding as well as scientific merit and feasibility.

_____ _____
Principal Investigator Signature Date

Appendix 9 – CTWG Reviewer Form

HSC CLINICAL TRIAL WORKING GROUP
REVIEWER SHEET

The HSC Clinical Trials Working Group received the proposed protocol:

Protocol Title:

Principal Investigator:_____ _____Yearly accrual goal - ___ Estimated time of accrual _____

Name of Senior Advisor and Rank, if applicable _____

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

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

Comments:

____ Abstract (lay language) _____

____ Introduction (background) _____

____ Objectives _____

____ Scientific Rationale and Merit _____

_____

____ Eligibility Criteria _____

____ Treatment Plan and/or 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.)

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

Probability that study results may lead to further extramural funding: **5** – High, **3** -Medium, **1**- Low

Reviewer's Scientific Priority Score: ____ Funding score:_____ **Overall score**:_____

Reviewer: _____ Date of Review: _____

A sheet of paper may be attached for additional comments.

Elements to consider during review

Title appropriate for study

Appropriate inclusion/exclusion

Age range of population(s)

Inpatient vs. outpatient

Accrual Rate

Stratification criteria

Randomization scheme

Schema/schedule

Appropriate doses for population

Dosing adjustment criteria

Duration of therapy

Concurrent therapy restrictions

Surgical guidelines

Radiation therapy guidelines

Frequency and appropriateness of assessments (labs; physical exam; radiological procedures; etc.)

Side effect criteria

Off-study criteria (voluntary withdraw; adverse reaction, non-compliance)

Post-treatment evaluation

Study calendar

Specimen collection schedule and procedures

Specimen processing/storage procedures

Consent Form

Community based engagement project

Evidence of practice support-suitability

Project funded by WVCTSI pilot grant

Appendix 10 – CTWG Pharmacy Review Form

HSC CLINICAL TRIALS WORKING GROUP
MEDICATION CHECKLIST

The HSC Clinical Trials Working Group has received the proposed protocol:

Protocol title:

Principal Investigator:_____ Yearly accrual goal - _____ Estimated time of accrual _____

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

Appendix 11 – CTWG BioStat Review Form

HSC CLINICAL TRIALS WORKING GROUP

STATISTICIAN SIGN-OFF SHEET

The HSC Clinical Trials Working Group has received the proposed protocol:

Protocol Title:

Principal Investigator: **Yearly accrual goal -** **Estimated time of accrual**

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.

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