MOUNTAIN STATES HEALTH ALLIANCE
RESEARCH DEPARTMENT

PROCEDURAL MANUAL
FOR CLINICAL RESEARCH
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| ORGANIZATION CHART               | 18 |
These Standard Operating Procedures apply to:

**MSHA Corporate**

**Tennessee:** FWCH, IPMC, JCCH, JCMC, SSH, UCMH, WPH, Niswonger Children’s Hospital, New Leaf, Kingsport Day Surgery (a separate legal entity managed by MSHA), Princeton Transitional Care, Unicoi County Nursing Home

**Virginia:** DCH, JMH, NCH, RCMC, SCCH, Clearview Psychiatric Unit, Francis Marion Manor Health & Rehabilitation, Green Oak Behavioral Health (Geriatric Behavioral Health Inpatient Program – DCH), Norton Community Physicians Services (NCPS), Community Home Care (CHC), Abingdon Physician Partners (APP)

**BRMMC**

**Home Health/Hospice**

**ISHN**

**Wilson Pharmacy, Inc.**

**Mountain States Pharmacy at Norton Community Hospital**

A copy of the Standard Operating Procedures (SOP) for the MSHA Research Department will be provided to all research personnel including, but not restricted to, Principal Investigators, sub-investigators, research nurses, research associates, assistants and others involved in any clinical trials at MSHA at the start of their responsibilities in clinical research. Receipt of the SOP copy by each researcher will be documented by their signature on a receipt form and will be maintained on file in the MSHA Research Department office. Research personnel must visit MSHA website periodically to review updated or newly posted SOP’s.

The SOP will be updated as necessary and a copy of the revised document will be posted on MSHA Intranet and Internet web page. Separate detailed SOPs accompany the main Procedural Manual. They must be reviewed and signed by research personnel.

**GENERAL ADMINISTRATION:**

A. **Department Staffing:**

The research department is staffed by a Corporate Director (CD), research assistant as needed to implement various research protocols.

B. **Research Staff Employment:**

Research staff is identified from applicants for advertised research positions. Potential candidates for MSHA Research department are interviewed by the CD and Chief Medical Officer over Research, and where applicable, by the Principal Investigator. Internal research staff can be identified by other MSHA departments and interviewed by the Manager of department, and where applicable, by the Principal Investigator.

Prior training in clinical research, research-related techniques and procedures are desirable but not required. Protocol-specific research training is provided on the job.

C. **Orientation:**

This is provided to all new hires through the MSHA Research Department and is arranged by the MSHA Human Resources Office and Research Administrative Assistant at the start of an individual’s employment.
D. **MSHA Required Training:**

General MSHA mandatory training includes but is not limited to Generic Laboratory Safety Training, Building Safety and Blood Borne Pathogens training, all offered through the MSHA Learning Management System.

E. **Research Related Training:**

Investigators, sub-investigators and all research team members receive training in the following areas after they have completed orientation and MSHA required training and **prior** to initiating activities/responsibilities on clinical protocols.

1. **Clinical skills:**

   Training is provided, as needed, through the MSHA Research Education sessions and/or via Investigator’s Meeting/Training provided by industry sponsors of clinical trials. Some training is also provided through the Collaborative IRB Training Initiative (CITI) program.

2. **Human Subjects Protection Training:**

   Training is provided by the CD first in house for new team members in Good Clinical Research Practices, Federal Drug Administration (FDA) requirements, International Conference on Harmonisation (ICH) guidelines and National Institutes of Health (NIH) regulations, followed by web-based MSHA and/or NIH-mandated “Human Participant Protection Education” for researchers, and via Investigators Meetings and Training provided by sponsors of industry-sponsored trials. All investigators and staff must complete MSHA required research training and Certification prior to initiating research activities. The Corporate Director of Research Department provides training in the Informed Consent process and Health Insurance Portability and Accountability Act (HIPPA) requirements. This is an ongoing education process.

3. **Specimen Processing, Storage and Shipping:**

   The CD or a designee, instructs a new team member in Occupational Safety and Health Administration (OSHA) requirements and safe handling of biological specimens. If new research team members are not proficient in phlebotomy, they are provided on the job training and practice. The CD or an experienced team member provides training in biological sample processing and preparation for shipping. International Air Transportation Authority (IATA) web-training and certification is highly recommended.

4. **Data Collection, Forms Completion and Data Entry:**

   Training in completion of required source documents and filing of informed consent and other items in the patient chart is provided by the CD or a designee. Study specific training in data collection, forms completion and data entry is provided by either the CD or study sponsor and utilizes case report forms, the internet, or other sponsor provided data collection/transmission methods.

5. **Study Specific Training and Procedures:**

   The Corporate Director (for Class A studies), study sponsor and/or Principal Investigator provide training in protocol and study requirements either in house
or at Investigator Training meetings. Study specific training in procedures (some examples include study-specific blood pressure monitoring, EKG, body fat measurements, stat hemoglobin checks using HemoCue unit) is also done either in-house by the CD or by the study sponsor at Investigator training meetings.

6. Radiation Safety:

Clinical tests that require use of radioisotopes require initial staff training by the Office of Environment Health and Safety. This is provided prior to start of a research protocol that requires such testing. The CD will document such training and communicate this to the Office of Radiation Safety and provide ongoing, annual training in radiation safety.

7. Continuing Education:

Continuing education is recommended for all members of the research team but is only required if necessary to maintain professional licensure requirements for job performance. The specific area for on-going training will be determined by job requirements, by the educational qualification of the team member and licensing requirements. Medical and Nursing professionals will obtain continuing education credits (CEU) per requirements in areas that will be applicable to the research setting or in areas of their interest such as Advanced Cardiac Life Support (ACLS) accreditation. Physician team members will be responsible for arranging and paying for the training on their own. That applies to research staff outside of MSHA Research department. Additional research specific CEUs may be available and recommended by the CD and these will be paid through research funds and will be taken during work hours. For non-medical, non-nursing staff such as Research Associates who do not require CEU credits, continuing education will be provided in areas of their interest and of potential application to improving their job performance. Two (2) sessions per year will be offered to each employee. These may be taken during office hours. Vacation time will not be charged for attendance at these training sessions. Staff should also involve themselves in to the continuing education programs available to them twice a year through MSHA and/or East Tennessee State University (ETSU) programs.

8. Access to data:

Research staff may request a temporary or permanent access to MSHA databases based on design of the each study. MSHA Corporate Director will evaluate a request and notify MSHA HIPAA officer, when appropriate. Usage of identifiable and/or de-identifiable data in accordance with IRB-approved protocol may require an additional set up of access to MSHA S-drive/research data.

Requirements for request of access to medical records are outlined in policy Release Of Medical Records For The Purpose Of Research.

ROLES AND RESPONSIBILITIES:

A. Principal Investigator (PI): The Principal Investigator is responsible for all aspects of the review and conduct of the research; receiving appropriate training and documentation of the same; ensuring adequate staff training has been provided and sufficient resources are available for
conduct of the research; appropriate patient recruitment and for performing physical exams **prior** to subject enrollment to ensure that it is safe for them to participate in the trial; review and confirmation of subject eligibility for research trial; ongoing oversight of the trial unless delegated to the CD; and medical management of subjects, adverse event reporting, and quality data collection until study close out. The ETSU IRB and MSHA Research Department accepts terms outlined in the ETSU Conflict of Interest (COI) form. Signed COI form must accompany IRB submission. Any changes must be reported.

B. **Sub-Investigators (Sub-I):**

The sub-investigator is responsible for receiving and documenting appropriate training, for performing physical examinations and the medical management of subjects enrolled in the research study. Sub-PI must complete COI form.

C. **Corporate Director (CD):**

This individual provides administrative and managerial oversight for the department and is assisted by other team members as appropriate. The CD is responsible for ensuring that all approved sites (including any satellite sites) meet study facility requirements and staff at these sites receive information/training regarding Good Clinical Practice (GCP) guidelines, human subject protections, the research protocol, their role and communication during the course of the trial. The Corporate Director is also responsible for hiring or terminating staff and this will be done in conjunction with the Chief Medical Officer over research and a Human Resources Representative. Additional responsibilities include review and acceptance of new protocols with investigator recommendations, preparation of regulatory documents and review contracts, approval of study budget and management of study funds, study start-up with establishment of sub-contracts and collaborations, oversight of investigational product storage and inventory, staff training and oversight for subject recruitment, and ensuring that all protocols are implemented appropriately and quality data collected in an ethical and timely manner keeping subject safety in mind. The CD will also provide ongoing communication with staff and Principal Investigators via regular staff meetings. Responsibilities may vary based on design of studies (Class A, B or C).

D. **Research Staff:**

Clinical Research Coordinators (CRC) is responsible for providing clinical oversight, mentoring and assisting research associates and for providing some training to new staff. They are also responsible for bringing medical issues to the attention of the Principal Investigator (PI) and/or Unit director in the absence of the PI and physician sub-investigator. CRC will make an assessment of unexpected adverse conditions and either inform and consult with the PI, follow standing orders if appropriate, or send the patient to the Emergency room or request/perform emergency procedures as appropriate with the event, training and skill level. These are documented and institutional review board (IRB) informed by the CRC or PI. In the event the CRC is unavailable to make such assessment, the PI or other medical doctor/doctor of osteopathy (MD/DO) should be notified immediately or patient escorted to the Emergency Department as appropriate. Items of a non-medical nature involving clinic operations should be brought to the attention of the CD and PI at the earliest convenience based on the urgency. All other responsibilities are as indicated below.
For Class A (refer to Attachment A) the Corporate Director assigns a team staff member to attend the Investigator’s meeting along with Principal Investigator or sub-investigator to receive training in the protocol and protocol specific procedures.

Class A (also recommended for other classes):

Prior to each study start-up all research team members are cross-trained in all protocols being implemented in the department. When other researchers (East Tennessee State University [ETSU], satellite or other research personnel) participate in the research, the MSHA research team member with primary responsibility for the protocol will be designated as the Study Coordinator (SC; also known as Clinical Study Coordinator or Coordinator) as referenced in the MSHA Standard Operating Procedures for Clinical Research. A second MSHA team member will serve as back-up SC. As a standard practice, a SC and a back-up SC will assigned to all research protocols (both federally funded and Industry sponsored). This allows for un-interrupted implementation of protocol specific visit requirements and patient care during employee absences or during heavy patient loads. Protocol specific training for industry sponsored trials is provided to the investigator and one team member at the Investigator’s Meeting; to all available staff on site by sponsor representative during site initiation meeting, via teleconference or through web-based training programs. The CD provides additional training on an as-needed basis. The primary study coordinator (PSC) and the PI are responsible for subject recruitment and for the informed consent process. The PSC or PI will present informed consent at the first clinic visit. Copy of Informed Consent Form must be filed in patient’s medical record. The PSC is responsible for scheduling and conducting study visits per protocol, for arranging dispensing of study medication through MSHA pharmacy (Class A or B3 studies), dispensing and/or administering investigational drugs to research participants unless it is required to be administered via intravenous (IV) or other way. In that case, to maintain the integrity of the line the facility nurse working with that subject draws blood from the line, administers investigational product, monitors the subject while they are undergoing treatment, and reports any adverse event to the PSC per MSHA SOP. Other responsibilities are per the Delegation of Responsibilities form provided by Industry sponsors and filed in the study Regulatory Binder or as assigned by the CD or PI. These responsibilities include but are not restricted to maintaining source and study documents/charts per study and/or clinic requirements; maintaining study drug inventory for drugs stored at the unit; ongoing monitoring of subject for adverse events and reporting these to the sponsor and director of the department in a timely manner; maintaining patient stipend accounts and making payments to subjects per informed consent payment schedule; ongoing communication with Principal Investigator, CD and the research team as appropriate; query resolution; study monitoring visits and assistance with study close-out. Travel to other MSHA facilities approved by the Institutional Review Board (IRB) and involved in the study may be required. Security measurements for transferring research data must be in place. Travel from the main campus to and from other facilities can be reimbursed based on the current rate for mileage reimbursement. Travel directly from home to the facility will not be reimbursed unless it exceeds daily travel to and from the main office. The CD approves reimbursement requests and the administrator makes payment to staff.

Study drug and study materials required for studies conducted at the MSHA properties will be taken to the center either by MSHA research staff or will be delivered by the
MSHA Designated pharmacy. The majority of study related documents will be maintained in the MSHA Research Department with some exceptions. The CD can approve storage of the study related document on MSHA sites.

Nursing staff at all MSHA locations:

Staff at all MSHA approved research locations assist the Research team members by providing information, exam rooms and biological sample processing facilities; and identifying location for courier pick up of samples to be mailed to outside study labs. All study visit scheduling, study visits, related procedures, drug dispensing and/or administration, data collection, subject reimbursement for parking and/or travel expenses is done by the research team members, generally by the PSC. At the Johnson City Medical Center (JCMC) Regional Cancer Center location, the MSHA nurses perform such procedures as have been approved through the MSHA and these could involve study drug administration and observation for any adverse reactions immediately following or up to an hour post-dose in addition to other specified research activities. Radiology staff can perform certain research responsibilities based on a sponsor-provided and documented training.

E. MSHA Research Audits and Compliance Committee:

Meets on quarterly bases and/or as necessary to review findings on currently open studies and/or work on future proposals. This committee leads audit procedures.

STUDY START-UP:

A. Review of Protocol and Investigator’s Brochure (IB):

PI and Assigned Pharmacist both review the protocol and information in the IB to confirm the study is important and relevant for the chosen patient population and that the study design is safe and acceptable; PI confirms that sufficient subjects are available either from the MSHA practice, from the community or through collaborations with other physicians to make it feasible to accept study. Based on this review, the study is then accepted or declined by CD.

B. Research Budget:

CD negotiates MSHA research budgets directly with sponsor or with the agency funding the study. The rates for study related activities are determined by standard charges used by most sponsors and commensurate with the actual time spent by members of the research team in each of these activities or in keeping with the cost to site. The current overhead rate set by the MSHA is negotiated with the sponsor in most cases. A lower budget and/or lower overhead rate may be acceptable if the research is deemed to be of sufficiently high scientific or clinical merit by the Investigator. MSHA Finance Department is responsible for creating a detailed study budget with assistance of assigned trained study coordinator; assigning research rates; setting up of the study-specific research account at MSHA Accounting department which will be required for Class A study. IPLAN 926 must be used during scheduling any service for patients participating in research.

Finance department is responsible for developing PI payment plan, when applicable. Research Team develops a Delegation Plan. Both documents require primary review by CD, prior to final approval from Finance department. Both documents are part of a study addendum (PI and/or Sub-PI subcontract). Copies of these documents must be
kept at MSHA Finance department. Finance department must present quarterly financial reports to MSHA CD of research for Non-standard of care procedures (NSOC) Annual report must include SOC and NSOC activities.

C. **Regulatory Documents:**

These documents are prepared by the CRC with assistance from other team members and submitted in a timely manner to the sponsor. These documents include but are not restricted to the FDA form 1572, Protocol acknowledgement/acceptance form, financial disclosures, COI, Curriculum vitae of members listed on the 1572 and medical/nursing licenses.

D. **Institutional Review Board (IRB) Approval:**

Protocols are submitted by the CRC to the Central IRB if they are industry chosen or to ETSU IRB if funded by federal agencies or are investigator initiated. Documents submitted include but are not restricted to the signed Submission Cover page, Central IRB submission form (if applicable), Study Protocol, Investigator's Brochure, Form 1572 (if applicable), Informed Consent form, HIPPA form (if applicable) including MSHA language Advertisements (if applicable), CVs of PI and sub-investigators (if applicable), medical licenses (if applicable), and other relevant documents. Industry sponsored protocols are first submitted to ETSU IRB for review and permission prior to submitting to Central IRB. Once approved, ongoing communication is directly with Central IRB for continuing review, amendments, Serious Adverse Events (SAE) reporting etc. In case if PI (Class B, C) received Central IRB approval for multicenter study and seeking for service support from MSHA, he/she still needs to notify ETSU IRB by completion of X-form via ETSU IRB Manager, MSHA administrative approval may be granted based on ETSU IRB trial recognition letter. Central IRB fees apply and are the responsibility of the sponsor.

Federally funded and investigator initiated protocols are submitted only to ETSU IRB and ongoing communication, continuing review, submission of amendments, SAE reporting etc. is directly with them. ETSU IRB fees are waived for NIH, Department of Defense (DOD) and small private grants. Research team members may assist the PRC with preparation of these documents.

PI must notify MSHA Research department of completion of the study.

E. **Confidentiality Agreements (CDA) and Research Contracts:**

Based on service arrangements for Class B and C, but for all Class A studies, the Confidentiality Agreement is approved by the MSHA Legal Department prior to the PI and MSHA Administration signing it. Once a CDA has been signed a complete study protocol is sent to PI or CD by the sponsor for Industry sponsored research. There is no CDA for Federally funded studies as these are investigator-initiated in most cases. MSHA Request for Research Form must be completed (via ETSU IRB Manager) and approved prior to opening of the study at MSHA. The MSHA Legal Department assists CD in negotiation of the language of the contract and finalizes it after the CD, with assistance from the Finance Department, approves budgets/payment schedule and IRB approves the research.

Authorization from the ETSU IRB Provost and appropriate department (example: Dean of Internal Medicine) is required for accepting new studies with ETSU facilities as a
study staff. In this case, CDA must be presented for review at ETSU prior to submitting back to sponsor.

In case of potential conflict of interest reported by Principal Investigator, MSHA Research department will evaluate report and present a management plan developed by ETSU Provost to Chief Medical Officer over Research. Research Audit and Compliance Committee may review this report, if necessary.

**STUDY MANAGEMENT:**

A. **Source Documentation:**

Source documents are defined as original documents where information has been written the first time a subject is interviewed or procedures are done. A source document may be a Clinic Progress Note, an EKG print out, an original lab report, a letter, a hand written note on a piece of paper, the informed consent form, the HIPPA form, patient’s medical history form, print out from testing equipment, research study worksheets used to obtain/document data collected from subject, etc. Such documents are filed in the patient research chart unless the sponsor requires them to be in the study subject binder. The research chart is kept separate from the clinic chart and is located in cabinets in locked research offices with access limited to research and assigned clinic staff.

Release of medical records may be granted by MSHA Medical Record department based on the IRB and MSHA Research department approvals.

B. **Patient Related Record Keeping:**

All patient information is filed in either the patient research chart or study binder, per study requirements. Case report forms, copies of lab reports (or originals if sponsor requires these), copies (or originals if sponsor requires this) of informed consent and HIPPA and other study related patient documents are filed in subject binder. In case of using identifiable data, all arrangements must be outlined in ICD. All necessary measurements to protect Protected Health Information (PHI) must take a place.

In case of using transferable de-identifiable data, Master List including some elements of PHI, **must** be kept at a secure e-folder assigned to the research team on **MSHA S-drive/Research data**, with password-protected access. Access must be terminated based on PI notice of completion of the study.

C. **Regulatory Documents:**

All regulatory documents are filed in study binders supplied by the sponsor or created by research team. They are subject of review during completion of the regulatory audits by MSHA Research department.

D. **Contracts and Financial Disclosures:**

Contracts are kept in separate financial files by the CRC. Financial disclosures and Conflict of Interest forms are kept in the Research regulatory binder if the study sponsor requires that.
E. **Study Correspondence:**

   All communication with the sponsor and their affiliates is filed in the Study Binder under the correspondence section. Correspondence with the research central lab is filed under the Laboratory section (if one exists).

F. **Monitoring Visits:**

   The study monitoring occurs in a private setting with access to a telephone. The PSC participates in the monitoring visits for industry-sponsored research. Others assist as needed. The CRC (PSC) is responsible for responding to queries related to regulatory documents. The study monitor documents the monitoring visit. For federally funded research studies monitoring is done by the investigator through regular meetings with the research team, by the PSC on an ongoing basis and by the Data Management/Data coordinating group or by the CD.

G. **Drug Storage and Accountability:**

   For MSHA studies, Investigational drug inventory is maintained with the Investigational Pharmacy. If study design requires, then the Pharmacist needs to be un-blinded to medication assignment in a blinded study.

   The drugs are stored in locked cabinets or refrigerators in the locked MSHA Pharmacy. Access to these cabinets or refrigerators is limited to the designated pharmacist. Research team members may collect Investigational Product (IP) from pharmacy during completion of the study visit.

   Drug accountability for **investigational drugs** or sponsor provided drugs is done using study provided forms. For Federally funded studies or other non-industry sponsored studies, the data coordinating center, a study manager or the CD may review drug accountability records periodically and at the end of the study. In the case of **blinded** drugs stored and dispensed by the Investigational Pharmacy, the Investigational Pharmacy maintains the drug inventory log and completes the dispensing and accountability records. The study monitors review these records and destroy study drug as appropriate at intervals during the study.

   For non-investigational drugs dispensing is recorded in the patient research chart and in the Drug Dispensing binder with Lot number and date of expiry with dispensing team member’s initials or signature.

   For research visits conducted at the MSHA locations, the investigational drug can be stored at that location with sponsor approval or is taken to that location at each visit by the assigned pharmacist or research team. If the drug is to be administered via the intravenous (IV) line, particularly in case of “Blinded study drug” the drug is couriered over from the main MSHA Investigational Pharmacy by a team member or assigned pharmacist on the same day of the day of drug administration/study evaluations.

   For external studies (Class B), PI is responsible for maintaining a proper storage and distribution of the IP.

H. **IRB Communication:**

   Communication with ETSU or Central IRB is ongoing during the course of the study and documented in the IRB section of the sponsor provided Regulatory Binder or in a separate binder dedicated to IRB communications for a federally funded study. All IRB submissions, correspondence, approval letters, panel roster, and guidance documents
are under one section unless there are separate sections for these. MSHA Research department must be notified of the major events requiring IRB notifications for external (non MSHA) studies.

I. **Investigational New Drug (IND) Safety Reports:**
These are sponsor-provided reports and are filed in house for both industry and federally funded studies. A summary report is provided to ETSU IRB at the time of annual continuing review of the research per their guidance document, or a list of the reports is provided to the Central IRB. If Central IRB desires the full report, copies of the requested reports are mailed to them. For federally sponsored studies any data safety monitoring board reviews/reports that are available are submitted to ETSU IRB. These may be available at the data-coordinating center for multi-center trials and are requested from them prior to annual review of the research.

J. **Study Close-out:**
Research studies are closed out after all enrolled subjects at local site have completed all protocol required visits/procedures and any required follow-up, or when a study is terminated early and after all enrolled subjects have completed final evaluation, all queries have been resolved to sponsor satisfaction, and data has been reviewed and signed by the investigator. In the case of investigator-initiated research, the study will be closed out at the end of the grant period after all enrolled subjects have completed evaluations and appropriate follow-up has been arranged for them. IRB must be notified of study close out. The Accounting Department deactivates the study account once outstanding bills are paid and final payment is received from the sponsor.

**SUBJECT MANAGEMENT:**

A. **Screening:**
Potential subjects for a research protocol are identified by the PI, sub-investigators, or CRC from clinic practice(s) either through a MSHA database search or through referrals from other physicians. Suitable candidates are then contacted directly by the physician at a clinic visit or by the CRC to determine the patient’s interest in participation in the research trial. For some studies individuals respond to approved, posted/published advertisement or are referred to the research team by outside physicians. All such patients are evaluated for possible participation in the trial.

B. **Recruitment:**
Self-referred individuals and referrals are contacted on the phone and study information is provided to determine if they are interested in participating in the research and whether they are willing to come to the clinic to review the study information and informed consent document. In some cases, a telephone interview is conducted using an IRB approved script to determine if a patient is interested and eligible to come in for screening tests. Interested participants are invited to come to the clinic to hear details about the study and to review the consent form and HIPPA document. If they agree, a clinic visit is scheduled at a time convenient for both the interested participant and the team members.

C. **Informed Consent:**
The clinic visit is conducted in a private exam room. The study details are first reviewed orally with the participant. This is followed by a detailed review of the
informed consent form (ICF) and the HIPPA document. The participant is given sufficient time to read these documents in private. The participant may take the unsigned forms home to review and discuss the research with family or others. All questions are answered to the individual’s and family member’s satisfaction. The investigator is also available to answer any questions that require more detailed explanation. If the participant agrees to participate, their understanding of the study and its requirements and subject responsibilities are gauged through questioning regarding the salient points of the ICF and HIPPA such as the name of study drug, the sponsor, why the study is being done, why they are being considered for the study, the visit schedule, how the investigational drug or treatment will be administered, their right to withdraw at any time during the study without any prejudice, who will have access to their personal identifiable information (including MSHA representative), and the compensation they will receive for travel and parking expenses.

Once the participant has complete understanding of the research he or she may accept or decline participation in the trial. Those who volunteer to participate in the research study by signing the ICF have study screening procedures initiated the same day if convenient for the individual. A copy of the signed ICF and HIPPA document is given to the subject at this time. The consent process is documented in the Clinic note. Signed original ICF is filed in the research chart. Signed copy of ICF must become part of the medical record if:

a. ICF signed at MSHA
b. Research participant is scheduled for an investigational procedure (example: surgery, PET scan with contrast as IP)
c. Screening procedures proceed per protocol.

D. Confirmation of Subject Eligibility:

Results of screening tests and procedures are reviewed against study inclusion/exclusion criteria by two (2) team members (PI and PSC, CD and PSC, or PSC and another team member) to confirm that the subject meets study enrollment/randomization criteria and has none of the exclusions. This is a requirement for Class A studies, and optional for Class B studies. In some cases, the sponsor may grant a waiver for some exclusionary criteria and this is documented in the clinic note. In other cases the sponsor or an expert may review some of the results and determine subject eligibility for the trial. Once subject eligibility is confirmed, he/she is enrolled into the study. This is documented by the PI in the subject’s clinic chart as well as the research chart.

NOTE: Upon registration subject to the study, research staff must submit MSHA Research Subject Registration form to MSHA Research department (via fax).

E. Study Visits and Investigational Product Administration:

Research team members schedule subjects for study visits per protocol requirements. These visits are conducted under the direct oversight of the PI and/or CD and the CRC at approved locations. Oral study drugs are dispensed to subjects per protocol and clear instructions are provided to subject orally and in writing. Subjects, in most cases, receive the first dose in the clinic and are observed for immediate side effects for at least one half hour before leaving the clinic. The subject is also instructed to call the research staff immediately if any adverse effects are observed or to go the nearest
emergency room if adverse effects are severe. The subject is advised to inform the emergency room staff that they are participants in a research trial and provide the name of the study doctor and a telephone number for both the doctor and the research office. This information is provided to the study participant in writing. In case the study drug is administered by injection or IV line, it is administered in the clinic at a time when the PI or another physician is available in case of a medical emergency. Research staff or MSHA nurses observe the subject for at least one (1) hour post dose for any reaction to the study drug. If the study drug is to be taken by the subject at home, clear instructions are given to the subject by the MSHA research staff and understanding of instructions is confirmed by questioning the patient regarding the instructions. Written contact and study information is given to the subject before they leave the clinic or dialysis center.

F. Specimen Collection, Handling, and Shipping:

Trained MSHA team members (or clinic nurses) collect biological specimens required for the study per protocol. Research staff delivers samples for processing as required by protocol to the MSHA laboratory. Designated lab staff must receive training prior to processing lab samples. Trained personnel may ship samples to an outside lab per study requirements.

NOTE: Some exceptions may be considered for external researchers.

G. Data Collection and Data Entry:

Research data is collected at the protocol and interim visits through measurements, interview, questionnaires, procedures, evaluations and other means as appropriate. These are documented per study requirements either on case report forms (CRF) in the subject binder, via the Internet or via other means per study requirements.

H. Adverse Event Reporting:

All adverse events of non-serious nature will be documented in patient chart, CRF or database with full details and will be followed to resolution if possible. Resolution data will be obtained by the end of study to determine if further follow-up is necessary.

NOTE: PI must be notified.

I. In the case of Serious Adverse Events (SAE) as defined in the FDA guidelines and per IRB requirements, the event is reported to the sponsor, the PI and the IRB (if event is unexpected, occurs to patient enrolled at MSHA, and may be study drug related) within twenty-four (24) hours of knowledge of event. This is done via the serious adverse event form, by telephone or by letter. All appropriate documents relating to the SAE are obtained as soon as possible and forwarded to the sponsor and IRB, if applicable. The investigator determines causality between the investigational product and SAE. If the event is related to the study drug, or is fatal, this is reported immediately to both the IRB and the study sponsor and relevant documents obtained speedily. All information identifying the subject is blackened out and only study number and initials or study code and the date of the event are noted on these documents. If SAE is an expected outcome of concomitant medical conditions, IRB may be informed via the continuing review submission form per their requirements. If SAE occurred at MSHA at a time of receiving service, MSHA research department must be notified.
J. **MSHA Audits:**

MSHA representatives are allowed to complete necessary audits (regulatory, financial). It is expected to receive full cooperation by research staff. Audits could be completed on randomly selected studies or based on reported findings of non-compliance.

**DATA MANAGEMENT:**

A. **Industry Sponsored Trials:**

Data collected for industry-sponsored trials will be entered on CRFs or into study database via the internet, or through electronic data capture systems using modems. Study data will be managed and analyzed by the study sponsor. They may or may not release the findings to sites.

B. **Federally Funded Studies:**

Data collected for research may be in the form of laboratory data, CRFs, or other. These are all eventually stored in computerized systems for analysis. The data management group or data coordinating center, or the PI in case of investigator initiated research, is responsible for the statistical analysis of data, for generating timely reports, for submitting these to the sponsor and publishing its findings if appropriate.

C. **Record Storage:**

Records (research charts, study regulatory binders, patient study binders) are stored in locked cabinets or on shelves in locked offices with entry restricted to research team members. Confidentiality of subject information is maintained at all times and waste paper with any subject information is shredded or destroyed immediately.

D. **Archiving Research Records:**

It is a requirement that research data be kept available for review and audit for two (2) years following withdrawal of an IND (Investigational New Drug) application or until the sponsor approves its destruction. For Class A studies, all source documents and study data is boxed and kept in storage off site with Fireproof Storage Company in Johnson City, Tennessee. MSHA Research department maintains the log. These documents are retrieved at the time of an audit and made available to auditors.
QUALITY ASSURANCE:

A. **Industry Sponsored Studies:**

   An on-going audit of data collection and study related documentation is performed by the sponsor representative or a Contract Research Organization (CRO) at regular intervals during the study. This audit covers 100% of study related documents.

B. **Federally Funded Studies:**

   An internal audit is done annually for a random sample (3%) of study documents for patients enrolled in federally funded or investigator initiated research. This internal audit serves as an internal check for quality assurance and is done by a team member not directly involved with data collection from these patients. Audits may also be done by the data management or by the data-coordinating group for multi-center trials. Emphasis is on informed consent process and documentation, confirmation of subject eligibility by review against inclusion/exclusion criteria and timely reporting of serious adverse events. Findings from the audit are summarized in an audit report and filed in an Internal Audit Binder kept in the MSHA Research Department. A copy of the report is distributed to all the research staff and an action plan is put in place to correct and resolve discrepancies and avoid future occurrences.

C. **External Federal Audits:**

   The NIH or other agencies funding the research may conduct external audits. They review all study documents (source documents, subject recruitment, subject eligibility, regulatory documents etc.) as deemed necessary.

   **NOTE:** Studies approved at MSHA are subjects of audits by MSHA representatives for monitoring regulatory, protocol and financial compliance.

LINKS

Release of Medical Records For The Purpose of Research, MR-900-055
Mountain States Health Alliance - Categories of Research, Attachment A
Administrative Procedures, Attachment B
REPORTING STRUCTURE FOR CLASS A

EXECUTIVE VICE PRESIDENT AND CHIEF MEDICAL OFFICER, MSHA

VICE PRESIDENT/CHIEF MEDICAL OFFICER
WASHINGTON COUNTY, TENNESSEE

CORPORATE DIRECTOR

SITE PI ↔ PI → SUB-I

RESEARCH NURSES, RESEARCH COORDINATORS AND ASSISTANTS

____________________________________________ __________________________
Executive Vice President, Chief Medical Officer, MSHA Date

____________________________________________ __________________________
Corporate Director, MSHA Research Department Date

I have read and agree to comply with this procedural manual for clinical research.

____________________________________________ __________________________
Research Staff Member, MSHA Research Department Date