THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER

SOP-20: Single and Multi-Site Investigator Initiated Trials

1. Objective

To ensure that the Principal Investigator (PI) and all research team members assisting in the conduct of clinical research are informed about their obligations and responsibilities as they pertain to Good Clinical Practices (GCP), the investigational plan, applicable regulations, guidances, and institutional policies. This Standard Operating Procedure (SOP) applies to the written procedures followed by all members of a clinical research team involved in the conduct of human subjects' research at The Ohio State University Wexner Medical Center (OSUWMC), hereafter called the investigational site. These detailed instructions promote compliance in conducting clinical research.

SOP-20 describes the process for conducting Single and Multi-Site Investigator-Initiated Trials (IIT).

Attachments include:

A: Investigator-Initiated Study Management Checklist
B: Clinical Trials. Gov Guidance

2. Responsibility

The College of Medicine Center for Clinical Research Management (COM-CCRM) develops, implements, and maintains SOPs. The need to write a new or revise an existing SOP is based upon changes to federal regulations, guidelines, institutional policies, or procedures. These documents will be provided to departments and research teams conducting human subjects' research. Departments or research teams may develop additional research SOPs or a Research Procedure Addendum (RPA) to expand on an existing SOP, however this need should be limited.

The PI is ultimately accountable for all clinical research activities and is responsible for the appropriate delegation of tasks to individuals with adequate training and education to perform such tasks. It is the responsibility of all members of the clinical research team involved in supervising, managing, or conducting study-related activities to follow the SOPs. The clinical research team may include but is not limited to the following members:

Research Team Members

Principal Investigator (PI)	Clinical Research Coordinator (CRC)
Sub-Investigator or Co-I (Sub-I or Co-I)	Clinical Research Assistant (CRA)
Clinical Research Manager (CRM)	Other Research Staff as appropriate
Clinical Research Specialist (CRS)	Administrative and Support Staff

3. Definitions and References

Please refer to the SOP Glossary document for detailed definitions of commonly used clinical research terminology.

4. Procedures

A. Mentoring New Investigators

It is strongly recommended that, if the investigator is new or has little experience with the conduct of clinical research at OSUWMC, the Department Chair and/or Division Director identify a mentor in the applicable field, preferably during the study design phase. Center for Clinical and Translation Science (CCTS) may also provide study-related mentorship.

B. Project Design and Protocol Creation

A protocol may require, but is not limited to, creation of the following:

1. A project design that will meet scientific and ethical review requirements.
2. Informed Consent Form describing potential research participant risks and benefits, as applicable *(See SOP 07: Informed Consent Development*).
3. Corresponding study budget and coverage analysis to ensure adequate funding to complete the study, as applicable.
4. Case Report Forms (CRFs) or Data Collection Forms (DCFs), either paper or electronic, developed based on the protocol and in collaboration with the Principal Investigator and biostatistician, as applicable. Generally, CRFs will not be used as source documents. If data is entered directly into the CRFs, this must be clarified in the study regulatory files.

Please refer to the Office of Responsible Research Practices (ORRP) Investigator Guidance for additional information regarding the development of a research protocol and Informed Consent Form templates.

The Principal Investigator should also consult with a statistician to verify their statistical outcomes and ensure endpoints can be met based on the proposed patient number. Statistical services and vouchers may be requested by contacting the Center for Clinical and Translational Science (CCTS).

C. Project Feasibility Assessment

Before beginning a new research proposal at OSUWMC, the investigator(s) should complete a protocol feasibility assessment to ensure that there are adequate resources and potential participants to successfully conduct and complete the study (*See SOP 04: Protocol Feasibility)*.

Investigator-initiated research requires an increased level of regulatory support and clinical coordination. Each investigator should ensure that they have experienced regulatory and clinical support to help conduct the research study and maintain compliance throughout the course of the study *(See Attachment A: Investigator-Initiated Study Management Checklist*).

D. Investigational Product

In the event the investigator-initiated research protocol includes the use of a drug, device, and/or biologic, the Sponsor-Investigator is responsible to determine if it is currently approved for use by the FDA for the study's therapeutic intent. The Sponsor-Investigator can contact the FDA for assistance in determining if the protocol needs to be reviewed or is exempt from IND or IDE requirements. The criteria for determination are based on the applicable FDA therapeutic division requirements.

E. Study Funding

The Principal Investigator may need to identify external or internal funding if necessary to support the research plan. If funding is required, the investigator should develop a study budget and coverage analysis to ensure adequate financial resources are available to conduct the study (e.g., staffing, supplies), as applicable. Assistance with budget development may be provided by the appropriate University Offices [e.g., Grants Management Office (GMO), Office of Sponsored Programs (OSP), etc.]. Effort tracking may be requested even if the study is unfunded.

F. Study Implementation and Management

If the research proposal is determined to be an Applicable Clinical Trial, then the Principal Investigator will be responsible for creating, updating, and maintaining study records, in accordance with rules established by the FDA and NIH that require most clinical trials to register, and report results on ClinicalTrials.gov (42 CFR 11 Clinical Trials Registration and Result Information Submission) *(See Attachment B: Clinical Trials.Gov Guidance)*.

Implementation

The Principal Investigator or designated study team member should meet with all study team members involved in the conduct of the trial to ensure protocol training is completed for the Principal Investigator, Co-I(s), and delegated research team members, including any ancillary services, as applicable (*See SOP 08: Site Initiation Visits and SOP 09: Protocol Implementation*). This meeting will review the following, but is not limited to:

1. Written IRB approval for the study and supportive study documents have been received, final documents are available to the study team and essential regulatory documents are completed, organized, and filed appropriately *(See SOP 6: Essential Document Management)*.
2. Ensure that proper delegation of authority *(See SOP 2: Delegation of Responsibility)* and appropriate university and GCP training including, but not limited to, CITI training (Human Subjects Protection and Responsible Conduct of Research), HIPAA and eCOI are completed for each member of the study team.
3. The budget is finalized, and the contract is executed with appropriate OSP account created, as applicable.
4. The site is in receipt of an adequate Investigational Product (IP) supply and that records are maintained for delivery and inventory, as applicable and appropriate IP security and storage are available *(See SOP 15: Investigational Product Management)*.
5. Review the recruitment and screening plans for subjects and ensuring that these methods are IRB approved, as applicable *(See SOP 10: Subject Screening and Recruitment)*.

Operations and Management

Along with the Principal Investigator, the research team members are responsible for maintaining protocol compliance and ensuring the following, including, but not limited to:

1. No research activities are performed prior to obtaining informed consent and that the consent discussion is properly documented, as applicable *(See SOP 11: Obtaining Informed Consent)*.
2. All documentation and reporting of protocol deviations and adverse events for the trial are complete and reviewed by the DSMB and IRB of record as applicable *(See SOP 12: Protocol Compliance and SOP 13: Adverse Event Reporting)*.

3. Biospecimens and data collected during the trial are collected, stored, and retained appropriately *(See SOP 14: Research Specimen Management and SOP 16: Data Management)*.

G. Monitoring Plan

For FDA-regulated studies, the Code of Federal Regulations (21 CFR Part 312 and 812) mandates that the sponsor of a drug, device, or biologic research trial provide independent monitoring of the information relating to their research trial (this is independent from the function of a Data Safety Monitoring Board (DSMB) or a Medical Monitor). It is the responsibility of the Principal Investigator to identify a monitor and create a monitoring plan that describes how the trial will be reviewed for regulatory compliance as required by the IRB. Please refer to the CCTS DSMB Training Manual for Investigator Initiated Studies for additional information on the development of a monitoring plan and DSMB development.

H. Study Termination

1. The Principal Investigator or delegated research team member will notify the IRB of record, the Research Billing Office (RBO) and the Office of Sponsored Programs (OSP), as applicable, when the study has been closed. ClinicalTrials.gov should also be updated with final study information, as applicable.

2. Upon closure of the study, the Principal Investigator will maintain all research related records according to federal regulation and university policies *(See SOP 16: Data Management)*.

I. Multi-Site Investigator-Initiated Trials

When overseeing an Investigator-Initiated Trial with external site(s), the Principal Investigator has additional responsibilities beyond those listed above. The OSU Principal Investigator is responsible for the management of information to ensure the protection of subjects for activities that do not occur at OSUMC.

If the research is subject to the Common Rule requirements and/or National Institutes of Health (NIH) single IRB (sIRB) mandate, Ohio State will either serve as the sIRB of record or rely on the designated sIRB of record. Please refer to ORRP's policy on Collaborative and Multi Site Research and guidance for Single IRB (sIRB) for Multi-Site Research for additional information.

The Principal Investigator must ensure the necessary resources are in place to adhere to these procedures. This may include but is not limited to a project manager, study coordinator(s) and/or a Contract Research Organization (CRO).

In addition to the obligations listed above, the Principal Investigator of a Multi-Site Investigator-Initiated Trial is also responsible for the following, but not limited to:

1. Identify qualified investigators and participating institutions with the ability and resources to participate in the protocol. Ensure personnel are qualified through training and experience.
2. Oversee the conduct of the study at all participating institutions and monitor its progress. This may include, but is not limited to, tracking patient accrual from all participating institutions, performing registration and/or randomization, and holding regular teleconferences with all participating institutions.
3. Ensure the protocol and other essential documents are provided to each participating site, with version control and subsequent modifications clearly documented.

Investigational Product
Investigational agent(s) will be supplied or made available to each participating site, as applicable. This may involve direct shipment from drug manufacturer to participating sites or coordinate drug transfer with OSUWMC per Investigational Drug Service policy.

Study Funding
The Principal Investigator will need to ensure inter-institutional agreements, contracts or sub-awards are in place to address:

1. How participant information and/or research samples are sent between participating institutions and the Coordinating Center, (e.g., MTA or DUA), if applicable; AND
2. How to administer appropriate payments to sites and other units as applicable.

The Principal Investigator will develop procedures to require study investigators and others associated with the study to identify financial and other conflicts of interest and share this information with the appropriate regulatory authorities.

Study Implementation and Management
The Principal Investigator or designated study team member will obtain documentation of IRB approval for all participating sites involved in the research. Generally, the IRB approval documents and a fully executed Clinical Trial Agreement (CTA) are obtained prior to the Site Initiation Visit (SIV). All participating site's essential documents (e.g., HSP, GCP, IATA, CV, medical licenses, 1572, IRB approvals, etc.) should be collected in a Master Trial File and maintained by the Coordinating Center.

Implementation
Along with the Principal Investigator, the delegated research team members are responsible for the following, including, but not limited to:

1. Assess site accrual goals for each participating institution, monitor subject accrual and define plan of action for sites not meeting their accrual goals.
2. Ensure all applicable local and regulatory reporting requirements are met.
3. Act as liaison with all participating institutions, regulatory agencies, and the IRB of record, as applicable. Maintain active oversight of protocol conduct.
4. Ensure that all data points (e.g., CRFs) are shared with the coordinating center in a compliant manner.
5. Ensure all sites and research team members are familiar with applicable OSUMC policies and responsibilities when OSU is the IRB of record.
6. Establish regular communication (e.g., convened meetings, teleconferences, emails, etc.) with all participating sites and research team members to discuss research progress and protocol/subject-related issues. This should include distribution of minutes and reports for meetings.
7. Collaborate with site investigators and/or research team members to create the consent document template(s) for IRB review.

Trial Operations and Management

1. Provide timely feedback to sites on items like enrollment, eligibility (inclusion/exclusion), forms completion, missed visits, data entry.
2. Have a procedure for documenting and handling protocol deviations/violations and AE/SAE determination as defined in the protocol and ORRP Policy Event Report. Provide reports for participating sites on items such as upcoming site visits and unresolved protocol deviations and other deficiencies.
3. Distribute IND or other safety reports, as applicable, to each participating site(s) for reporting to IRB or other regulatory bodies.

Study Termination

At the close of the trial the Principal Investigator or delegated research team member(s) are responsible for the following, including, but not limited to:

1. Ensure that all data queries are appropriately resolved prior to data base lock, as applicable.
2. Ensure that IP or other provided equipment is returned or destroyed per protocol and documented appropriately.
3. Conduct a financial review of payments distributed to participating sites, as applicable.
4. Collect the notices of closure from all participating institutions and maintain in the Master Trial File.
5. Document participating site's document retention plans.
6. Prepare for manuscripts and presentations tracking, preparation, review, communication, and submission (including interaction with pharmaceutical and device collaborators, as appropriate).

5. Applicable Regulations, Guidances and Policies

Regulation/ Guidance/Policy	Title
21 CFR 11	Electronic Records; Electronic Signatures
21 CFR 50	Protection of Human Subjects
21 CFR 54	Financial Disclosure by Clinical Investigators
21 CFR 56	Institutional Review Boards
21 CFR 312	Investigational New Drug Application
21 CFR 812	Investigational Device Exemptions
45 CFR 46	Protection of Human Subjects
45 CFR 160	HIPAA Privacy Rule
45 CFR 164 Subparts A and E	HIPAA Privacy Rule
OSU Office of Responsible Research Practices HRPP	Additional Requirements for Clinical Research: ICH GCP
OSU Office of Responsible Research Practices HRPP	Documentation of the Informed Consent Process

OSU Office of Responsible Research Practices HRPP	Event Reporting
OSU Office of Responsible Research Practices HRPP	Informed Consent Process and the Elements of Informed Consent
OSU Office of Responsible Research Practices HRPP	Noncompliance
OSU Office of Responsible Research Practices HRPP	Privacy and Confidentiality
OSU Office of Responsible Research Practices HRPP	Recruiting Methods, Recruitment Materials, and Participant Compensation
OSU Office of Responsible Research Practices HRPP	Research Involving Human Subjects
OSU Office of Responsible Research Practices HRPP	Research Involving Investigational Drugs
OSU Office of Responsible Research Practices HRPP	Research Involving Medical Devices
OSU Office of Responsible Research Practices HRPP	Responsibilities of Principal Investigators, Co Investigators, and Key Personnel
OSU Office of Responsible Research Practices HRPP	Review of Research by Convened IRB
OSU Office of Responsible Research Practices HRPP	Suspension and Termination of IRB Approved Research
OSU Office of Responsible Research Practices HRPP	Vulnerable Populations: Students, Employees, and Adults Unable to Provide Consent
OSU Office of Research	Research Data Policy
OSU Office of Research Compliance	Human Gene Transfer
OSUWMC	Use of Patient Information by Hospitals and Medical Staff
OSUWMC	Patient Information & HIPAA Requirements
OSUWMC	Information Security Policy
OSUWMC Investigational Drug Services	IDS Policies and Procedures

COM Office of Research Compliance	ClincalTrials.gov Compliance SOP
ICH GCP E6(R2)	Guideline for Good Clinical Practice: E6 Integrated Addendum
FDA Guidance for Industry	Investigator Responsibilities- Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009
FDA Guidance for Industry	FDA Inspections of Clinical Investigators Information Sheet, June 2010
FDA Guidance for Industry	Adverse Event Reporting to IRBs- Improving Human Subject Protection, January 2009
FDA Compliance Program Guidance Manual	Program 7348.11 Bioresearch Monitoring: Clinical Investigators and Sponsor Investigators
FDA Guidance for Industry	Oversight of Clinical Investigations- A Risk-Based Approach to Monitoring, August 2013
FDA Guidance for Industry	Sponsor- Investigator- IRB Interrelationship- Information Sheet
FDA Guidance for Industry	Frequently Asked Questions- Statement of Investigator (Form FDA 1572), May 2010
FDA Guidance for Industry	Electronic Source Data in Clinical Investigations

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