***Investigational Product (IP)***

1. **PURPOSE**

This Standard Operating Procedure (SOP) describes the regulatory responsibilities, processes, and procedures pertaining to the accountability of the Investigational Product (IP) (including placebos, investigational devices, and combination products).

**(MANDATORY LANGUAGE)**

1. **SCOPE**

This SOP applies to all members of the research team involved with the management of the IP for a clinical trial. The process for non-IP (not under study) products is not within scope of this SOP. The responsibilities of UM faculty/staff that act solely as the Sponsor of a clinical trial are also out of scope for this SOP.

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional details necessary to further define the scope of this SOP]*

1. **POLICY**

This Standard Operating Procedure supports the Good Clinical Practices (GCP) guidelines established by the International Conference on Harmonization (ICH):

ICH GCP Guidelines E6

**Principal Investigator:**

**4.6 Investigational Product(s)**

Section 4.6 of the ICH GCP guidelines focuses on the Investigational Product(s), including

4.6.1 *responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.*

Please see additional regulations in Section 4.6, includingSections 4.6 - 4.6.6.

**4.7 Randomization Procedures and Unblinding**

**Sponsor Investigator:**

In addition to the above regulations, the PI and/or Sponsor of the trial should follow GCP guidelines, including:

**5.12 Information on Investigational Product(s)**

**5.13 Manufactureing, Packaging, Labeling, and Coding Investigational Product(s)**

**5.14 Supplying and Handling Investigational Products(s)**

FDA Regulation ☐ N/A

*[If this SOP is not intended for FDA regulated clinical trials, check the N/A box]*

**Principal Investigator:**

The PI of the trial should abide by the following 21CFR regulations:

**Per 21CFR part 312.61** Control of the investigational drug

**Per 21CRF part 312.62** Investigator recordkeeping and record retention

**Per 21CFR part 312.69** Handling of controlled substances

**Per 21CFR part 812.140** Records

**Sponsor Investigator:**

In addition to the above regulations, the PI and/or Sponsor of the trial should follow 21CFR part 312.5, including:

**Per 21CFR part 312.57** Recordkeeping and record retention

**Per 21CFR part 312.59** Disposition of unused supply of investigational drug

**Per 21CFR part 812.5** Labeling of investigational devices

University of Michigan Health System (UMHS)

*A study involving an Investigational drug or biologic that is conducted using UMHHC facilities must be reviewed by the Research Pharmacy. Per pharmacy Policy, investigational drugs used in humans in the UMHHC must be stored and dispensed by IDS pharmacy. Exceptions (waiver of IDS involvement) may be allowed in situations where it can be shown that storage or dispensing of the drug by IDS presents a hardship to the investigator, to study subjects or to the conduct of the study. In these cases, Research Pharmacy shall assure storage, dispensing and inventory control criteria are met by auditing these processes. (This was taken from eResearch, however, Research pharmacy policy link is included here.)*

*Policy: 400.05* [*http://ummcpharmweb.med.umich.edu/i/Policies/tabid/71/Default.aspx*](http://ummcpharmweb.med.umich.edu/i/Policies/tabid/71/Default.aspx)

**(MANDATORY LANGUAGE)**

 **Additional Regulations or Policies ☐ N/A**

*[Optional: Insert any additional project, department, sponsor, institution, state or federal policies that apply]*

1. **DEFINITIONS**

COMBINATION PRODUCT: The term includes:

1. A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
4. Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

GOOD CLINICAL PRACTICE: A standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

INTERNATIONAL CONFERENCE ON HARMONISATION (ICH): A joint initiative involving both regulators and research-based industry representatives of the European Union, Japan and the USA in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines

INVESTIGATIONAL DEVICE EXEMPTION (IDE): An investigational device is a device, including a transitional device that is the object of an investigation. Approval by FDA for investigational device exemption (IDE) permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully across state and international boundaries for the purpose of conducting investigations of that device. (FDA 21CRF812)

INVESTIGATIONAL NEW DRUG (IND): A drug permitted by FDA to be tested in humans but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing. Use of investigational drugs requires application to the FDA and is usually limited to subjects enrolled in clinical studies covered by an Investigational New Drug agreement with the FDA. (IRBMED)

PRINCIPAL INVESTIGATOR (PI): The lead scientist or engineer for a particular well-defined science (or other research) project, such as a laboratory study or clinical trial.

SPONSOR: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

SPONSOR-INVESTIGATOR: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject.)

 **(MANDATORY LANGUAGE)**

*[Optional: Insert any additional definitions for technical or special terms used within the Standard Operating Procedure that may not be familiar to the lay reader]*

**Note:** Many of the definitions above were obtained from the IRBMed Glossary. These definitions were current as of 22-Sep-2015 and are subject to change. Please see the [IRBMed Glossary](http://medicine.umich.edu/medschool/research/office-research/institutional-review-boards/guidance/glossary) for the most current definitions and additional guidance.

**(MANDATORY LANGUAGE)**

1. **ROLES AND RESPONSIBILITIES**

**Principal Investigator/Designee**

An individual filling the role of Principal Investigator (PI) is accountable for the management and accountability of the IP in a clinical trial at the site. The Principal Investigator or Designee shall be responsible for the following activities:

* Assigns the duties for investigational drug accountability to the UMHS Research Pharmacy or a similar organization that complies with local, state and federal laws
* Ensures proper steps are taken to obtain a waiver when not utilizing the UMHS Research Pharmacy
* Ensures the clinical research team follows all local, state, and federal requirements for the investigational drug when not using the Research Pharmacy**.**

See Research Pharmacy Policy 400.05:

<http://ummcpharmweb.med.umich.edu/i/docs?xsdid=4637&file=RP_Inspection_of_other_ID_storage_areas.pdf> (Note: This includes mandatory audits by the Research Pharmacy.)

* Authorizes and delegates to individuals the authority to prescribe IP
* Ensures that the IP is only dispensed according to the approved protocol and to participants that are appropriate
* Follows all applicable randomization procedures, including unblinding/unmasking of IP
* Ensures that participants understand the correct use of the IP and provides IRBMED approved patient education material when necessary
* Maintains a record of the IP products returned from participants, and ensures they are delivered to the research pharmacy
* Ensures investigational devices are properly stored and managed by the clinical research team including receipt of shipment, inventory at the site, dispensation/use by each participant, final dispensation, number of devices that have been repaired, returned to the sponsor or otherwise disposed of and the reason for the repair or disposal. (Note: the Research Pharmacy does not provide accountability for devices, however, they may do accountability for combination products)
* Receives and provides necessary training prior to using investigational devices
* Ensures that the Biomedical Engineering Unit (BEU) has assessed all devices for safety and tagged or registered all devices at UM

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional details regarding the responsibilities of the Primary Investigator/Designee*]

**Sponsor-Investigator/Designee**

A UMHS Investigator filling the role of the Sponsor Investigator assumes the responsibilities of the Principal Investigator as described above and ***in addition***, is responsible for the following:

* Determines whether or not an IND and/or IDE application must be filed with the FDA prior to use of an IP in a clinical trial
* Submits the IND and/or IDE application to the FDA
* Oversees the management of IP product supply (procurement, distribution, accountability, disposition)
* Arranges and provides randomization and unblinding/unmasking procedures regarding the IP
* Selects appropriate qualified, prescribing investigator(s)
* Provides investigational site(s) with all necessary materials to run the clinical trial (i.e. Instructions for the IP, the Investigator’s Brochure, etc.) and coordinates additional training as needed
* Ensures investigational site(s) have the appropriate approvals prior to shipping drug or devices to the site(s)
* Ensures monitoring is in place to review drug and device accountability at the site(s) during the life of the clinical trial
* Supplies tracking tools to participating sites and/or pharmacies (when needed) to facilitate management of inventory, shipping, storage, dispensing, disposal and return of IP
* Follows all local, state, ICH GCP, federal laws, and international laws (when applicable) for the clinical trial

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional details regarding the responsibilities of the Sponsor- Investigator/Designee*]

**Study Coordinator(s)/Designee**

An individual filling this role shall be responsible for the following activities:

* Maintains documentation of participants given IP
* Records details of the IP (e.g. dispensing, administration, return and/or disposal dates, etc.)
* Discusses with the PI concerns regarding the storage, use, safety, disposal or return of the IP that may arise during the clinical trial
* Reviews IP for expiration date and other issues that could affect the safety or quality of the IP
* Collaborates with the Research Pharmacy for the life of the clinical trial
* Ensures proper information is recorded and documentation stored regarding IP
* Assists study team with the storage and management of the investigational device
* Creates additional guidance or SOPS to help facilitate the management of the IP

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional details regarding the responsibilities of the Study Coordinator(s)/Designee*]

**Co-Investigator(s)**

An individual filling this role may be responsible for the following activities:

* Ensures that the IP is only dispensed according to the approved protocol and to participants that are appropriate
* Notifies the PI and applicable research team members of any concerns regarding the IP
* Follows all applicable randomization procedures regarding IP and unblinding/unmasking of IP
* Ensures that participants understand the correct use of the IP and provides IRB approved patient education material when necessary
* Maintains records of the IP product returns from participants and returns investigational drug back to the research pharmacy
* Receives and provides necessary training prior to using investigational devices, as needed

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional details regarding the responsibilities of the Co- Investigator(s)]*

**Additional Roles and Responsibilities**  **☐ N/A**

**(MANDATORY LANGUAGE)**

*[Optional: Insert any additional role(s) and responsibilities that apply to this SOP]*

1. **PROCEDURE**

**Non-University of Michigan Sponsor Initiated Clinical Trial Regulatory Obligations**

*[Describe the process to collect all necessary information from the Sponsor to submit necessary IP information in the IRB application (i.e. IB brochure, package insert, manufacturing information, etc.)]*

**University of Michigan Sponsor-Initiated Clinical Trial Regulatory Obligations**

*[Describe the process to collect and distribute all necessary information regarding the IP (i.e. IB brochure, package insert, manufacturing information, etc.) to all participating research staff.]*

**Investigational Drug Accountability**

*[Describe the process to document drug accountability (i.e. clinical trials will be managed by Research Pharmacy]*

*[When not using the Research Pharmacy, (waiver required) describe the process that the research team will follow in order to manage all necessary regulations (i.e. where will the drugs be kept, what type of logs will be maintained, etc.)*

*[Describe the process at the site to document additional steps in the drug accountability trail (i.e. delivery of study medications to participants and the returns.)]*

*[Describe the process when another Pharmacy or the UM Research Pharmacy (please note at UM they are not set up to do this, you must get their input prior to them agreeing to this) has agreed to be the central hub for shipping study drugs to other sites for a multi-site trial (i.e. will the PI or study team give the okay for them to release drug, Research Pharmacy will provide a pharmacy manual for sites, etc.)]*

**Investigational Device Accountability**

*[Describe the processes to store and manage the device used including the receipt of shipment, inventory at the site, dispensation/use by each participant, and final dispensation, why and how many units of the device have been returned the sponsor, repaired, or otherwise disposed of. Records of these should include dates, quantities, batch, serial numbers and expiration date (if applicable).]*

**Additional Procedures** **☐ N/A**

*[Optional: Insert any additional relevant procedures. Provide enough detail to ensure the procedure is consistently carried out, without providing so much detail that violations occur due to normal or expected variations in the work.]*

1. **REFERENCES**

FDA [Title 21 CFR 312.61 - Control of the investigational drug](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61>

FDA [Title 21 CFR 312.59 - Disposition of unused supply of investigational drug](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.59): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.59>

FDA [Title 21 CFR 312.69 - Handling of controlled substances](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.69>

FDA [Title 21 CFR 312.62 - Investigator recordkeeping and record retention](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.62>

FDA [Title 21 CFR 812.5 - Labeling of investigational devices](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.5): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.5>

FDA [Title 21 CFR 312.57 - Recordkeeping and record retention](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.57): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.57>

FDA [Title 21 CFR 812.140 - Records](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140): <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=812.140>

FDA Combination Products: <http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm118332.htm>

ICH GCP Consolidated Guideline – Part 4.6 Investigational Product (s) and Part 4.7 Randomization Procedures and Unblinding:

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

University of Michigan - Michigan Institute for Clinical and Translational Research (MICHR) - IND/IDE Investigator Assistance Program (MIAP):

<https://www.michr.umich.edu/services/regulatorysupport/miap>

University of Michigan - Michigan Institute for Clinical and Translational Research (MICHR) - MIAP - For Investigator-Initiated Medical Device Clinical Investigations - IND DECISION WORKSHEET (IND requirement or exemption determinations):

<https://www.michr.umich.edu/Uploads/Research%20Management/Regulatory%20Support/MIAP-IND%20Decision%20Worksheet_2-8-13.pdf>

University of Michigan - Michigan Institute for Clinical and Translational Research (MICHR) – MIAP - For Investigator-Initiated Medical Device Clinical Investigations - IDE DECISION WORKSHEET (IDErequirement or exemption determinations):

<https://www.michr.umich.edu/Uploads/MIAP-IDE%20Decision%20Worksheet_COMPLETE_FINAL_revd_9-09-2011.pdf>

University of Michigan - Michigan Institute for Clinical and Translational Research (MICHR) Study Coordinator Home - Regulatory Binder Essential Documents - Study Management Templates:

<http://www.umstudycoordinators.org/regulatory-binder-essential-documents/>

University of Michigan - Comprehensive Cancer Center -Clinical Trials Office - Study Drug Shipments Where the Univ. of Michigan is The Drug Depot:

<https://cto.med.umich.edu/SPGs/700/712%20Study%20Drug%20Shipments%20where%20University%20of%20Michigan%20is%20the%20Drug%20Depot.pdf>

[University of Michigan Health System - Department of Pharmacy Services - Research Pharmacy](http://ummcpharmweb.med.umich.edu/i/DepartmentSections/ResearchPharmacyService/tabid/78/Default.aspx)**:**

<http://ummcpharmweb.med.umich.edu/i/DepartmentSections/ResearchPharmacyService/tabid/78/Default.aspx>

1. **APPENDICES**

*[Optional: Insert any additional SOP appendices]*