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Hinda and Arthur Marcus Institute for Aging Research

Marcus Institute for Aging Research Interventional Studies: Start-Up Period

Institutional Guidelines

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1 Purpose

The purpose of this guideline is to provide a standard process for the startup of interventional studies at Hebrew SeniorLife (HSL). This guidance document provides standard procedures to promote compliance with applicable regulations and policies including but not limited to National Institutes of Health (NIH) requirements for interventional research. This approach will promote and help to ensure that Marcus Institute investigators and staff conduct studies with the highest ethical standards, ensuring data integrity and complete documentation.

2 Scope

This guideline applies to clinical trials and interventional studies conducted at HSL after July 1, 2019, which are being led by Marcus faculty and/or are being conducted by members of the HSL workforce. This guideline document focuses solely on the post-award period. It is applicable to studies for which HSL is the lead site and/or coordinating center, as well as multisite studies where HSL is a participating institution. Matters related to the general conduct of research that are non-specific to intervention studies (e.g., consenting subjects) are not the focus of this guideline. Links to guidance materials or Marcus Institute policies about such matters will be provided when appropriate.

3 Definitions

Clinical Trial: "A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcome" (NIH definition 2017). This term is synonymous with 'Study'."

Dashboard: A summary of current information about a project, which can include graphics to express trends in the progress of the project, usually in electronic format.

Data Use Agreement (DUA): A written satisfactory assurance between the covered entity and a limited data set recipient (e.g., an investigator) requiring agreement by the recipient to various terms, including that the data will only be used or disclosed for specific purposes, that the limited data set will be protected, that the recipient will notify the covered entity of any unauthorized uses or disclosures of which it becomes aware, and that the recipient will not identify the information or contact the individuals whose information comprise the limited data set.

Data Safety Monitoring Board (DSMB): An impartial group that oversees a clinical trial and reviews the results to see if they are acceptable. This group determines if the trial should change or close.

Intervention: includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject. (HHS)

Investigator: Principal investigator (PI) and any other person, regardless of title or position (including post-doctoral fellows, graduate students, collaborators, consultants, advisors, mentors, etc.), who is responsible for the design, conduct, or reporting of the Research (pending or awarded, sponsored or non-sponsored). This may include consultants and collaborators.

Manual of Procedures (MOP): A handbook that details a study's conduct and operations as well as facilitates consistency in protocol implementation and data collection across study participants and sites. It transforms the study protocol into a guideline that describes each step of the study and how it is to be executed.

Principal Investigator (PI): The Principal Investigator (PI) is the person responsible for completion of a funded project, directing the research and reporting directly to the funding agency. In the context of a clinical trial a PI may be an academic working with grants from NIH or other funding agencies, or may be effectively a contractor for a pharmaceutical company working on testing the safety and efficacy of new medicines. Co-Investigators assist the PI and may be responsible for specific aspects of the project.

Project Directory: The electronic file organization of documents and data for a study.

Protocol: A document that describes the background, rationale, objectives, design, methodology, statistical considerations, and organization of a clinical research project.

Regulatory Binder: The Regulatory Binder is an indexed collection of essential documents relevant to the Randomized Clinical Trial (RCT). While frequently referred to as a regulatory binder, it may also be called: Study Files, Investigator Files or Investigator Binder. The International Conference on Harmonization (ICH) Good Clinical Practice Guidelines (GCP) list documents generally considered essential for inclusion in the regulatory binder.

Statistical Analysis Plan (SAP): A technical document detailing the features of all aspects of the analytic plan, including all pre-specified primary and secondary outcomes.

4 Guideline Statement

It is the guideline of the HSL/Marcus Institute to ensure that any clinical trial or interventional study is conducted in compliance with relevant regulations and that all applicable safeguards and protections are incorporated into study plans.

5 Procedures

It is the PI's responsibility to ensure all aspects of the interventional study are conducted in accordance with guidelines stipulated in this guidance document, other relevant HSL and Marcus Institute Policies (e.g., Institutional Review Board) and the study's sponsor.

5.1 Project Life Cycle Overview

This guidance will address the first of three Phases of a funded project's life cycle; Startup. The Startup Phase begins once the study is funded and continues until the scientific portion of the project begins (e.g., participant recruitment, acquisition of data).

5.2 Start-up Procedures

5.2.1 Study Team

The PI designates study team members.

The Study Team typically includes but is not limited to the following roles, with some individuals fulfilling more than one role:

- Principal Investigators (PI) or multiple PIs
- Co-investigators or Investigator
- Project Director (PD)
- Biostatistician
- Programmer/Analyst
- Research Nurse
- Research Assistant (RA)
- Research Coordinator (RC)
- Ancillary personnel may also play a role but may not be considered 'team' members.
- All members of the study team must comply with relevant HSL and Marcus Institute procedures, policies and guidelines.
- Study team members will provide documentation of current human subjects' research training, professional credentials, and licensure (if required for their role in the study). CITI training (https://about.citiprogram.org/en/homepage/) is available for all study team members who are new to their roles or who would like a refresher.
- Additional study specific training will be completed by team members who have been delegated to perform activities requiring it, such as use of study specific equipment.
- Up-to-date documentation of all training will be kept in the Regulatory Binder (see below).

5.3 Human Subjects and Regulatory Issues

Investigators must comply with all regulatory and human subject protections requirements of the funding source (Federal, Foundation or Industry) and overseeing Institutional Review Board (IRB).

5.3.1 Institutional Review Board (IRB) review and approval

All research conducted by HSL investigators must be approved by the HSL IRB or officially ceded to another IRB for approval by the HSL IRB. As of January 2018, single site IRB review is required for all NIH

funded projects. All details regarding the HSL IRB policies and procedures can be found on the IRB section of the HSL website as well as the internal HSL "HUB".

5.3.2 Data Use Agreement (DUA)

A Data Use Agreement (DUA) allows a researcher to share a limited data set with a colleague or another person or entity not associated with the investigator's institution.

Refer to HIPAA, Section 45 CFR part 160 Subparts A and E of Part 164 for details of what type of data requires use of a DUA under the Privacy Act, and the best practices for compliance.

DUA policies, procedures and templates must adhere to the requirements of the entities sharing the data. For example, obtaining and using of Medicare claims data requires strict adherence to Research Data Assistance Center (ResDAC) guidelines and procedures (Medicare DUA). HSL has its own policies and procedures for applying, setting up, and maintaining DUAs (HSL DUA SOP). HSL investigators must work with the Director of Research Informatics, who oversees all DUAs at the Institute.

5.3.3 Data Safety Monitoring

The level of Data Safety Monitoring in a clinical trial varies study to study and depends on risk. Trials deemed to be minimal risk by the overseeing IRB and funding agency may require a Safety Officer (SO) rather than a full Data Safety Monitoring Board (DSMB). Decisions about the level of monitoring needed are determined by the funding agency and project officer, but may also be required by the IRB. It is advisable to check with the specific funding agency for sponsor-specific DSM requirements. For example, the National Institute of Aging provides guidance material and templates for DSM that should be followed when appropriate, NIA Data Safety Monitoring. For Sponsor-Investigators of IND Studies, additional forms and documents are required (e.g., FDA 1571). **Additional Links to guidance documents and templates are available in the Appendix.**

- The purpose of DSM is to ensure the safety of human subjects, relevance of the study question, appropriateness of the study, and integrity of the accumulating data. DSM requires reporting of all anticipated and unanticipated adverse events and protocol deviations. DSM also includes monitoring threats to credibility or the validity of the study related to slow rates of accrual, high rates of ineligibility after randomization, high rates of protocol violations, and high dropout rates.

- DSMB members or Safety Officer (SO) will be chosen by Project Officer on NIH funded studies. For industry sponsored studies the Sponsor determines the charter of the DSMB. The PI Investigator may be asked to suggest names. The DSMB is a formally appointed independent group, with at least 3 impartial external voting members, who are expert in the field of study, statistics and study design, and also includes the PI and study statistician. The DSMB typically reviews interim monitoring of the study data in an open, a closed and an executive session.

- Prior to study initiation the study team must complete the following in collaboration with the Project Officer: i. establishment of a DSMB or appointment of a SO, ii. Creation and approval of

a Data Safety Monitoring Plan, iii. Creation and approval of a Data Safety Monitoring Charter, iv. Creation and approval of a Data Safety Monitoring Report, and v. Creation and approval of a Data Safety Monitoring reporting procedures and meetings.

Further information is available in the E-Textbook.

5.4 Essential Documents and Tracking

5.4.1 Award Notification

Upon receipt of a Notification of Grant Award, the PI (s) should review entire project budget and its alignment with scientific milestones and meet the project's grant administrator before the initiation of study activities.

5.4.2 Protocol

The research protocol must be completed before the study commences and include key elements listed below. All changes to the study protocol during the study must be clearly tracked, and each update must be signed and dated by the Investigator, using appropriate version control and tracking. For Industry sponsored research any revisions to the protocol must be approved by the sponsor before submitting for IRB approval. Sponsors may require a particular protocol template. **See appendix for links to protocol guidance documents and templates.**

- Title Page (General Information)
- Background Information
- Objectives/Purpose
- Study Design
- Selection and Exclusion of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Adverse Events
- Discontinuation of the Study
- Statistics
- Quality Control and Assurance
- Ethics
- Data handling and Recordkeeping
- Publication Guideline
- Project Timetable/Flowchart
- References
- Supplements/Appendices

5.4.3 Statistical Analysis Plan (SAP)

The SAP provides detailed descriptions of the 'a priori' statistical analytic including analytic approach, pre-specified outcomes, and sample size/power estimates. The SAP may be included within the protocol of a separate document. It provides a rationale for the choice of methods, plan, and pre-specified guidance on interpretation of results. The Biostatistician will develop the SAP.

All changes to the SAP during the study must be clearly tracked, and each update must be signed and dated by the Investigator using appropriate version control and tracking. **See appendix for links to SAP guidance documents and templates.**

5.4.4 Manual of Procedures (MOP)

The Manual of Operational Procedures (MOP) is a handbook of instructions designed to guide the research team to successfully carry out all aspects of a particular research project according to that study's research protocol. The MOP transforms the protocol into a description of the exact procedures involved to implement every aspect of the RCT, and should be written prior to study startup

5.4.5 Regulatory Binder

A Regulatory Binder that contains essential documents for the clinical trial must be set up and maintained either electronically or on paper. Documents should be regularly updated with older versions maintained. Essential documents typically included in a Regulatory Binder are listed below. Multisite trials may have additional standardized elements in the site specific Regulatory Binder. Links to guidance documents and templates for many items are available in the Appendix.

Documents to Retain

- All IRB related documents
- DUAs
- Study Protocol and Supporting Documents
- Informed Consent Forms and Supporting Documents
- Source Documents
- Case Report Forms (CRFs) / Data Collection Tools
- Study Participant logs
- All DSM related documents
- Monitoring/Auditing
- Correspondence, Agendas/Meeting Minutes
- Study-related SOPs/MOPs
- Study Staff documentation (resume/CV and required certifications and conflict of interest)
- Drug/Device Accountability
- Regulatory Submissions

5.5 Register with Clinicaltrials.gov

- The clinical trial must be registered on Clinicaltrials.gov within 21 days of enrollment of the first participant. Failure to do so will jeopardize publication of trial findings in a top journal.
- Refer to HSL Marcus Institute Guideline on Clinicaltrials.gov Registration and Reporting Requirements

5.6 Set-up for Monitoring and Reporting

- Study Dashboard: A electronic **Study Dashboard** should be created using appropriate software that will allow for real-time monitoring of key milestones once the trial is initiated such as data regarding participant enrollment and follow-up, demographic characteristics of enrollees, completeness of data collection assessments, etc. The purpose of the Dashboard is to provide some of the content for routine (e.g., regular project meetings, NIH progress reports, DSMB report) and ad-hoc study reports.

5.6.1 Study Report(s)

- A Study Report shell should be created for presenting key data from the Study Dashboard which will be reviewed regularly at study meeting. **Links to guidance documents and example templates for Study Reports are provided in the Appendix**.

5.6.2 Meetings

- Study teams will meet regularly as appropriate (e.g., weekly, monthly) to monitor the trial progress.
- Different types of meetings involving different study team members are usually required (e.g., field staff, data management, full investigators).
- Prior to each meeting, an agenda will be drafted and sent to team members.
- During each meeting, minutes will be taken. Once minutes are available, they will be distributed to team members who were unable to attend.
- Agendas and minutes of all team meetings should be saved in the electronic file.

6 Reference Materials: Relevant HSL Policies

- Access to Closed and Archived Research Records
- Data Encryption Guideline
- Financial Conflicts of Interest Guideline
- HSL Responsible Conduct of Research Guideline
- Limited Data Sets and DUA
- Misconduct in Science Guideline
- Record Retention Guideline
- Request for Ceded IRB Review Form
- Sensitive Data Security Guideline
- Sensitive Data Sharing Guideline
- Sensitive Data Suppression Guideline
- Staff Changes and Data Access Guideline
- Sub-recipient Setup and Monitoring Guideline
- Technical Equipment Guideline
- Telephone Contact with Research Participants

7 Appendix: Useful Resources

General Clinical Trials Resources

1. NIH-NIA Investigator Toolbox
2. FDA Clinical Trials Guidance
3. USCF Clinical Study Management Guidance

DSMB

1. NIH-NIA Data Safety Monitoring Guidance
2. Harvard Catalyst Data and Safety Monitoring

Manual of Procedures (MOP)

1. NIA MOP Single Site
2. NIA MOP Multi Site

Protocol

1. NIA Startup Protocol Template
2. Clinical Trial Protocol Development-UCSF
3. NIH Clinical Trial Protocol Template

Regulatory Binder

1. Harvard Catalyst Essential Regulatory Documents Guidance and Binder Tabs

Clinical Trials.gov

1. How to Register your Study

Statistical Analysis Plan

1. Gamble, C, et al Guidelines for the Content of Statistical Analysis Plans in Clinical Trials; JAMA. 2017;318(23):2337-2343.

2. Marcus Institute E-Textbook Chapter

8 Document Properties

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Author:	Linda Godfrey-Bailey, Susan L Mitchell
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