Guideline for Developing a Manual of Operations (MOO)- RPG-05

Guideline

Purpose

The purpose of this Guideline is to provide advice to investigators and study staff regarding development of a study specific Manual of Operations (MOO).

Definitions

A study Manual of Operations (MOO) is a document that outlines the details of how to operationalize the scientific protocol and conduct all study-specific procedures. It is an essential tool that ensures accuracy and consistency in study implementation across study subjects, study sites and research staff over time. The MOO is also an important tool for the initial training of study staff and an invaluable reference when staff turnover occurs. All final approved versions of the study MOO should be version controlled by including a date in the footer, and maintained in electronic format. It is a ‘living’ document and should be updated as needed during the study to include new information, such as changes approved in amendments, and current contact information.

Procedure

A study MOO is highly recommended for all clinical research projects. A study MOO is typically drafted by CRC staff working in collaboration with the Principal Investigator (PI) and co-investigators for studies which the CRC is serving as the data coordinating center.

Contents

The content of the MOO varies significantly depending upon the type of research study, the scope of the study and the number of sites involved in the study. At a minimum, the following section should be included or described in the MOO, as appropriate. Each section is described below:
• **Study Overview:** This section includes a brief overview of the study, the study aims and objectives. An abstract prepared for the grant or proposal might serve as the study overview.

• **Study Organization:** As appropriate, for multi-site studies, include information regarding the governing structure and role of committees and subcommittees are detailed.

• **Staff Roles and Responsibilities:** Contact information for all study staff who interact with the research team and/or subjects/families are listed. Typically this includes the PI, co-investigators, project manager, study coordinator(s) and any relevant ancillary staff (i.e., laboratory personnel). In addition, staff members’ roles and responsibilities in the study should be described.

• **Subject Recruitment:** This section should explain the recruitment plan in detail - how subjects are to be recruited for the study, including how subjects will be informed about the study, who will approach subjects for recruitment, where the study population will be found, and types of pre-screening activities that will take place. This section should include details on how and when informed consent will be obtained and the URL link to the BCH Informed Consent Library (http://www.childrenshospital.org/research-and-innovation/research/clinical/office-of-clinical-investigation/informed-consent-library).

• **Screening:** The instructions in this section define the study population, each inclusion and exclusion Criteria, and describes the study screening activities. Details are provided to illustrate how and when each eligibility criterion should be evaluated prior to enrollment and what source documentation may be required.

• **Subject Enrollment:** This section includes the step-by-step instructions that are followed to enroll a subject into the study once s/he meets all eligibility criteria.

• **Randomization Procedures (for randomized trials only):** This section explains the randomization procedure for the study. If the study is blinded, the MOO must include the procedures required to maintain blinding and steps that must be followed in the event of intentional or inadvertent unblinding. For more specific information, refer to CRC Guideline for Developing Randomization Procedures, RPG-03.

• **Study Visit Schedule:** This section includes acceptable windows of time within which study visits should occur. This section should also include the study procedures/measurements that will be completed at each specific visit, and procedures to follow if a study visit is missed.

• **Study Measurements:** Detailed procedures should be provided to study staff to specify how to conduct study measurements. For example, these may include systematic procedures for measuring height, weight, head circumference, or blood pressure and the instruments that should be used. If special education, licensure, or protocol-specific training is required to complete the measurement, it should be described in this section.

• **Study Medication/Pharmacy Procedures (for drug treatment protocols):** This section includes details as to how the study medications (including placebos and
concomitant study medication, devices, etc., as applicable) are stored, how the drug is dispensed to the subject, and the role of the Research Pharmacy. For specific information, refer to CRC Guideline for *Developing Pharmacy Procedures for Clinical Trials, RPG-10*.

- **Case Report Forms (CRFs):** This section includes all current and final CRFs and data collection instruments, surveys, etc. Although there may be numerous versions and different drafts of the study CRFs over time, only the currently approved versions should be included in the MOO. All outdated versions of the CRFs should be archived electronically in a restricted access location. Final CRFs should only be accessible to study staff as PDF documents to prevent inadvertent or intentional alteration of the data collection instruments.

- **Question by Question (QxQ) Instructions:** A question-by-question instruction guide (QxQ) written for each CRF is recommended. These are also called ‘Case Report Form Completion Guidelines (CCGs)’. Each QxQ typically includes an introduction of general instructions regarding what the specific CRF is designed for; at which study visits the CRF will be completed; and who completes it. The instruction guide should also specify the primary source for the data recorded on the form (i.e., hematology lab report, discharge summary, operative notes). For more specific information, refer to CRC Guideline for *Developing Case Report Forms, RPG-02*.

- **Adverse Event Reporting:** The instructions provided in this section should describe the process of reporting adverse events. This may or may not include Serious Adverse Event (SAE) Reporting requirements as required by relevant agencies and institutional policies. For more specific information, refer to CRC Guideline for *Developing Adverse Event Reporting Procedures, RPG-01* and the CCI.

- **Sample Collection and Processing:** This section includes comprehensive instructions regarding how biologic samples are collected and processed, including shipping instructions where appropriate. It should include step-by-step instructions regarding all aspects of how the sample is to be collected, the supplies needed, how the sample is to be labeled and how the sample is to be processed to prepare for the analyses. If applicable, the instructions should also describe how the sample should be packaged and shipped. Procedures for maintaining a shipping log and specimen receipt log may also be included. This section should be as detailed as possible. For example, it is important to include timing issues, temperature specifications, a list of specific supplies needed, in addition to any other information that might be relevant to reduce the chance of error in processing. **Data Management:** The data management procedures should describe how data are to be collected and managed. This includes how study identifiers are assigned; where the ID assignment logs are located; the structure of the subject ID numbers; the modes of data collection (i.e., Electronic Data Capture (EDC) software); how data forms are completed, reviewed and filed or stored; and information on how missing data or invalid data on case report forms are addressed and resolved. It may also include data reporting plans, such as cut-off dates, plans for double-data entry, receipt of external data, and all other data management considerations.
• **Quality Assurance Procedures**: This section describes how quality assurance is maintained throughout the duration of the study. This customarily includes a description of study training and certification procedures, communication procedures and maintenance of a communication log, reproducibility studies, approaches to ensure the integrity of the data collected such as valid value and range checks during data entry and data security, regulatory and data verification audits, and on-going staff performance monitoring including site visits for multi-site studies.

**Development**

The development of the study MOO is a collaborative effort between the PI and the relevant study staff. When the CRC serves as the data coordinating center, CRC staff will collaborate in the development of the MOO. The MOO should be developed after reviewing the study protocol and outlining all the information that is needed to implement the study protocol. Details of these procedures are then developed by various staff with the appropriate expertise, and reviewed and approved by the study Principal Investigator.

The contents of the MOO is maintained as electronic documents and may be printed for reference (hard copy). Customarily, the MOO is divided into functional sections that contain specific information relevant to the various procedures and measurements. The first page of the MOO should include a Table of Contents detailing the sections and associated page number. Each section should be page numbered independently to facilitate future changes. A footer should be included on each page and contain the title of the section, the version date, and the page number.

**Implementation**

Once completed, the MOO will be made available to investigators and study staff working on the clinical research project. When the CRC is funded to serve as the data coordinating center, the MOO will be maintained by the CRC project manager assigned to the study. Other research staff working on the project will have access to relevant sections of the MOO based upon what role they have in conducting the research. A list of MOO recipients should be maintained by the study coordinator or project manager.

Changes to the MOO must be reviewed and approved by the PI and made to the master electronic document. All approved versions must be dated and maintained in the study archive. All hard copy MOOs in distribution must be updated by the study coordinator or project manager. All outdated hard copy versions of the MOO should be kept in the study archive by key study staff as a reference.
Related Content
Table of Contents – General Guidelines

I. Study Overview
   A. Study Aims and Objectives – Basis for study outcomes.
   B. Background and Rationale – Describe study rationale; detail previous findings related to illness/disease; define relative terms, acronyms, and abbreviations related to illness/disease.

II. Study Organization
   A. Participating Centers – Coordinating and study center(s), laboratories, etc.
   B. Administration and Governance – Committees, funding agencies, and data and safety monitoring boards.
   C. Roles and Responsibilities – Responsibilities of investigators and study staff defined.

III. Recruitment
   A. Inclusion and Exclusion Criteria – Eligibility criteria defined.
   B. Recruitment Approaches – Strategies for approaching and recruiting potential subjects.
   C. Informed Consent – Outline procedures for obtaining informed consent.

IV. Study Visits
   A. Study Visit Schedule – Visit schedule and activities entailed in each visit, baseline vs. follow-up visits, and visit windows.
   B. Treatment protocol – describe the intervention or treatment to be given where applicable.
   C. Randomization Procedures – Procedures to randomize subjects or groups to different study treatments and approaches for blinding where applicable.
   D. Study Close-out – Explanation of end-of-study activities, post-study follow-up.

V. Study Measurements and Data Collection Procedures
   A. Medical record abstracts.
   B. Administering surveys/questionnaires.
   C. Procedures and examinations.
   D. Specimens and sample collection procedures.

VI. Adverse Event Reporting
   A. Definitions, documentation.
   B. Reporting and follow-up procedures.

VII. Pharmacy and Drug Handling
   A. Research pharmacy procedures.
   B. Drug handling and administration procedures.
   C. Compliance with Hospital Policy – Research using drug/therapeutic agent implemented in a standardized way, in accordance with hospital policy.

VIII. Study Forms and Instructions for Form Completion
   A. Study forms.
   B. Question x Question instructions for completing the study forms.

IX. Data Management Procedures
   A. Overview of data flow.
   B. Data entry procedures.
   C. Form completion tracking.
   D. Data entry error resolution and editing procedures.

X. Quality Control
A. Training and Certification—Teaching standardized methods of data collection.
B. Staff Performance Monitoring/Site Visits— Oversight and periodic reviews.
C. Equipment calibration.
D. Laboratory quality control.
E. Communication procedures.

XI. Appendices
A. Recruitment materials.
B. Letters to study subjects, primary care providers, etc.
Example: Study Specific Table of Contents

I. STUDY OVERVIEW
   A. Specific Aims and Hypotheses
   B. Project Summary
   C. Time Line
   D. Coordinating Site Contact Information
   E. Study Collaborators
   F. Roles and Responsibilities

II. STUDY VISIT SCHEDULE AND FOLLOW-UP PROCEDURES
   A. Screening Visit
   B. Pouchoscopy Visit
   C. Study Drug Initiation and Pharmacokinetics
   D. Telephone Contact: Study Drug At One Week
   E. Study Midpoint (Two Weeks) Visit
   F. Telephone Contact: Study Drug at Three Weeks
   G. Exit Pharmacokinetics Visit (Four Weeks)
   H. Exit Pouchoscopy Visit (Four Weeks)
   I. Telephone Contact: Open-Label at Two Weeks
   J. Open Label Conclusion Visit

STUDY MEASUREMENTS AND DATA MANAGEMENT
I. Introduction
II. Data Collection
III. Data Management
IV. Study Monitoring
V. Adverse Events Monitoring

SECTION D: RANDOMIZATION PROCEDURE

SECTION E: FORMS AND QUESTION – BY – QUESTION SPECIFICATIONS
I. General Instructions
II. Telephone Pre-Screening - Form 1
III. Screening Visit - Form 2
IV. Labs – Form 3
V. Pouchitis Disease Activity Index (Pdai) – Symptom – Form 4
VI. Rating Form Of IBD Patient Concerns (Rtipe) - Form 5
VII. Pouchitis Disease Activity Index (Pdai) Pathology/History – Form 6
VIII. Inclusion Exclusion Criteria – Form 7
IX. Pharmacokinetics – Form 8
X. Telephone Follow-Up – Form 9
XI. Visit Follow-Up - Form 10
XII. Midpoint Visit - Labs – Form 11
XIII. Inclusion Exclusion Criteria – Open Label – Form 7a
XIV. Telephone Follow-Up Open Label Period – Form 12
XV. Open Label Physical Exam - Form 13
XVI. Adverse Events - Form 14
XVII. Serious Adverse Events - Form 15
XVIII. Withdrawal Form - Form 16

SECTION F: STUDY DRUG CHEMISTRY, MANUFACTURING AND CONTROL INFORMATION
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Disclaimer: Should Hospital and CRC policies conflict, Hospital policy will supersede CRC policy in all cases.