POLICY

The Beaumont Research Coordinating Center (BRCC) will provide advice to clinical trial investigators on protocol development, content and format. Upon request, the BRCC will review a draft protocol and provide comments to the investigator. The BRCC will prepare and/or review case report forms consistent with the elements of the protocol to assure data is collected to support the endpoints of the study.

This standard operating procedure (SOP) summarizes the fundamental elements of a sound research protocol and case report forms.

SCOPE

These policies and procedures apply to the BRCC and its employees who may be involved in protocol review activities.

RESPONSIBILITY

The BRCC will be responsible to review and contribute to the sections of protocols that apply to the services provided by the BRCC.

PROCESS OVERVIEW
Protocol Development

The Principal Investigator (PI) is responsible for the protocol and must approve any changes to the protocol prior to submission to regulatory agencies or committees.

A research protocol must provide a clear and complete description of the study and should include the following:

1. General Information
   - Protocol title
   - Name, contact information, title of PI
   - Name, contact information, of sponsor
   - Name, contact information of clinical laboratory, medical and/or technical departments supporting the study (i.e., central labs, core labs)
   - The test product IND or IDE number, if applicable

2. Background Information and Rationale
   - Hypothesis
   - Scientific justification
   - Previous clinical and non-clinical findings

3. Trial Objectives and Purpose
   - Primary and secondary endpoints

4. Research Design and Methods
   - Trial phase
   - Description of the type of trial (e.g., observational including case-control, cross-sectional, etc., or interventional including randomized, double-blind, placebo-controlled, etc.)
   - Details of the proposed intervention (e.g., surgery), investigational product (e.g., administration of drug), or data collection (e.g., survey)
   - Measures to reduce bias (e.g., randomization, blinding, etc.)
5. Potential Risks and Benefits
6. Study Subjects
   • Indicate the number of subjects to be enrolled.
   • Description of the study population
   • Inclusion and exclusion criteria
   • Removal criteria and procedures for subject withdrawal
7. Safety Monitoring
   • State the safety parameters; define Protocol Deviations, Adverse Events (AEs), Serious Adverse Events (SAEs), and Unanticipated Problems (UPs)
   • Indicate time points for review of study progress, Protocol Deviations, AEs, SAEs, and UPs
   • Identify how safety information will be assessed, recorded, analyzed, and reported; the PI should be responsible for assessing important safety events
   • A Data Safety Monitoring Plan, if the study involves greater than minimal risk to human subjects. Details of this plan should be outlined in the Protocol
8. Efficacy Measurements/Data Analysis
   • Description of how data will be analyzed
   • Description of the statistical methods to be used
9. Data Management
   • Determine the data management tools for the study
   • Source documents, Case Report Forms (CRFs)
   • Record retention
10. Quality Assurance Measures
    • Monitoring and audit frequency
11. Ethics
    • Human Investigation Committee (HIC)/Institutional Review Board (IRB) approval
    • Informed Consent
    • Protection of human subjects – a statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements
12. Investigator’s Statement
13. Publication Policy
14. References
15. Appendices
Protocol Review and Approval

1. Circulate draft protocol to appropriate BRCC team members assigned to review specific sections of the protocol pertinent to BRCC responsibilities.

2. Track changes will be used to edit the protocol. Changes may include editorial changes, typographical errors and appropriate operational, scientific or technical clarifications.

3. When the review is completed, the director or manager will be responsible to return the protocol back to the sponsor/investigator with BRCC recommendations.

4. Maintain a file with all draft protocols and correspondence regarding revisions until the protocol is finalized. Once finalized, retain approved clinical protocols and attachments, subsequent revisions and associated correspondence with regulatory authorities and other documents as required in the Regulatory Master File (RMF). Do not keep draft protocols or correspondence concerning the development of the protocol in the RMF.

Protocol Amendments

1. Review the amended protocol by the same method the original protocol was reviewed.

2. Track changes to the amendment so it is clear what changes were made.

3. Return the amendment to the sponsor/investigator. Ensure the recently amended Protocol has a new version number and date.

4. Should changes to a protocol result in changes to the CRF, assure the BRCC Data Managers have copies of the revised protocol in order to make appropriate changes to the CRF (see below).

5. Should changes to a protocol result in necessary changes to the Informed Consent and Authorization (ICAD), follow Beaumont Health System (BHS) policy to make appropriate changes to the consent.

6. Submit the amended protocol and ICAD (where appropriate) and a memo outlining the changes to the HIC or send it to the investigative sites instructing each to submit the amendment to its local IRB.

7. Verify investigators have submitted the amended protocol and additional documents to the local IRB(s) of record and other regulatory authorities where applicable by collecting the approval documentation. File with other regulatory material for each site in the RMF.

Development of Case Report Forms

1. The BRCC data management team will assign responsibility for designing the CRF.

2. Determine whether the CRF format is paper-based or internet-based.

3. Prepare a draft CRF (paper copy). Utilize the final approved protocol to determine data points.

4. Circulate the draft CRF to relevant parties (investigators, sponsors, etc.) to ensure the CRF captures all necessary data.
5. Incorporate recommendations, changes and additions from the investigators, sponsors, etc. into the CRF. Please note, data collection points not included in the protocol may not be added to the CRF (i.e., you may not include CBC results if the protocol does not require using CBC lab results).

6. The review process will be repeated as necessary until all parties approve a final version of the CRF.

7. Upon finalization of the CRF, the BRCC will perform data validations using contrived data to ensure CRF completion is clear, consistent and captures all data points.

8. Secure the signatures and approval dates of all reviewers in appropriate boxes on the document control form.

9. Prepare CRF instructions for the final approved CRF to ensure accurate completion.

10. When the protocol is amended, the CRF will be revised to reflect changes to the protocol. The revised CRF will be included in the review, approval and documentation process. CRF’s are not required to accompany their respective protocols throughout the regulatory review and approval processes (e.g., FDA), but may be included if desired.

11. Document any subsequent changes to the CRF as described in GA 102. CRF’s should be considered controlled documents.

12. Retain original and revised CRF versions.

APPLICABLE REGULATIONS AND GUIDELINES

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm

21 CFR 312.21 Phases of an Investigation
21 CFR 312.20 Requirements for an IND
21 CFR 312.23 IND Content and Format
21 CFR 312.30 Protocol Amendments
21 CFR 312.57 Record Keeping and Record Retention
21 CFR 312.62 Investigator Recordkeeping and Record Retention
21 CFR 312.68 Inspection of Investigator’s Records and Reports
21 CFR 314.126 Adequate and Well Controlled Studies


ICH E6 2.2 The Principles GCP
ICH E6 2.4 - 2.6 The Principles GCP
ICH E6, 2.10, 2.11 The Principles GCP
ICH E6, 4.5 Compliance with Protocol
ICH E6, 4.9 Records and Reports
ICH E6, 5.1 Quality Assurance and Quality Control
ICH E6, 5.4 Trial Design
ICH E6, 5.5 Trial Management, Data Handling and Record Keeping
ICH E6, 5.23 Multicenter Trials
ICH E6, 6.0 Clinical Trial Protocol and Protocol Amendment(s)
REFERENCES TO OTHER APPLICABLE SOPs

RI BRCC Policy #702 Documentation and Records Retention
“Guidelines for Writing Investigator-Initiated Protocols”, Beaumont Research Institute, Human Investigation Committee

ATTACHMENT

Clinical Protocol Contents and Review Checklist

Research Institute Compliance Committee Review Date: ____________________________

Corporate Administration Approval: ____________________________ Date: ____________
 V.P. of Research or Chief Medical Officer

Research Institute Board Approval: ____________________________ Date: ____________

Research Administration Approval: ____________________________ Date: ____________

Administrative Director

Research Institute Administration
Disclaimer: User must ensure that any printed copies of this policy/procedure are current by checking the policy and procedure web page before use.
## CLINICAL PROTOCOL CONTENTS AND REVIEW CHECKLIST

<table>
<thead>
<tr>
<th>Section &amp; Content</th>
<th>Comment</th>
<th>Complete</th>
<th>Initial</th>
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<tbody>
<tr>
<td><strong>A. GENERAL INFORMATION</strong></td>
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<tr>
<td>- Protocol title, number, and date</td>
<td>finalized</td>
<td>□</td>
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<td>- Amendment number(s) and date(s)</td>
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<td>- Name, address, phone #, e-mail of</td>
<td>Principal Investigator</td>
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<td>- Name, address, phone #, e-mail of</td>
<td>sponsor</td>
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<td>- Name and address, phone # of the</td>
<td>monitor (if other than the sponsor)</td>
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<tr>
<td>- Name and title of the person(s)</td>
<td>authorized to sign the protocol and amendment(s)</td>
<td>□</td>
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<tr>
<td>- IND number</td>
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<tr>
<td><strong>B. TABLE OF CONTENTS</strong></td>
<td>Include a list of appendices if applicable.</td>
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<tr>
<td><strong>C. BACKGROUND AND RATIONALE</strong></td>
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<tr>
<td>1. Hypothesis</td>
<td>Clearly state the research problem.</td>
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<tr>
<td>2. <strong>Scientific Justification</strong></td>
<td>Include the reasons for performing the study in the study's particular population. Indicate the magnitude of the problem, what the current knowledge is, possible solutions, and what information may be learned.</td>
<td>□</td>
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<tr>
<td>3. Preclinical Experience</td>
<td>Review the basic work leading to clinical testing.</td>
<td>□</td>
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<tr>
<td>4. Clinical Experience</td>
<td>Review previous clinical work with the investigational product and describe how the current protocol extends existing data. If an entirely new indication, discuss how this drug/biologic was considered for indication. Describe relevant information regarding pharmacological, toxicological and other biological properties and previous efficacy and safety experience.</td>
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### D. OBJECTIVES AND PURPOSE
State the objective(s)/purpose of the study.

- Correlate the objective(s) to the study design.
- Indicate the primary and secondary endpoints.

### E. RESEARCH DESIGN AND METHODS

5. **Overview**
   A brief overview of the study design to indicate how the study objectives will be achieved.

   Include:
   - Trial phase, description of the type of study (i.e., observational, double-blind, multi-center, placebo controlled, etc.), details of the specific treatment groups and number of study subjects in each group and investigative site, and the type, sequence and duration of study periods.

6. **Research Design & Methods**
   A description of the methods and procedures, discuss the rationale for the study design.

   Details of the proposed intervention (e.g., surgery), investigational product (e.g., administration of drug), or data collection, measures to reduce bias (e.g., randomization, blinding, etc.), a full explanation of the study visits/procedures in their order of occurrence, include timetable for screening, enrollment, study visits, and procedures, describe each visit separately as Visit 1, Visit 2, etc.

   Specific time points for subject visits might include:
   - Screening,
   - Randomization,
   - Baseline (day 1),
   - Interim visits (each visit listed and detailed separately),
   - Early termination,
   - End of therapy,
   - Post therapy follow-up

   Include a schedule of assessments and who will perform them; state where study visits will occur; explain storage accountability of the test article; state concomitant medications and /or treatments permitted and prohibited.

7. **Risks and Benefits**
   Include known and potential risks and benefits to the study participants.
### F. STUDY SUBJECTS

#### 8. Nature of Population
Briefly describe the nature of the subject population.

#### 9. Number of Subjects
State the number of subjects to be enrolled.

Identify the total number to be enrolled and how many at each investigative site. Identify “power” calculations.

#### 10. Subject Eligibility
List the criteria that will be used to determine the subject population

Care should be taken to develop these criteria. They should allow the inclusion of the desired target population, but should not be overly inclusive or exclusive. The criteria should be clinically relevant so that study results are applicable to the population affected.

**a) Inclusion Criteria**
Inclusion criteria may be based on:
- age,
- sex,
- race,
- diagnosis,
- method of diagnosis,
- diagnostic test result requirements,
- concomitant medication requirements,
- severity of symptoms and signs of the disease,
- the subject’s ability to perform study requirements and to give informed consent,
- other criteria.

**b) Exclusion Criteria**
Exclusion criteria may be based on:
- age,
- previous medical history,
- pregnancy, childbearing potential,
- concomitant or past therapy,
- severity of disease,
- current medical conditions,
- a timing requirement if the subject has recently participated in another,
- drug or alcohol abuse,
- upper/ lower limits of laboratory tests,
- other criteria.

#### 4. Rationale for the Inclusion/Exclusion Criteria
If there are any clarifications of the above criteria or special considerations
**Subject:**

**PROTOCOL AND CASE REPORT FORM DEVELOPMENT AND REVIEW**

**Standard Operating Procedure**

**Prepared By:**
Beaumont Research Coordinating Center, Research Institute

**Prior Issue Date:** 9/24/13

**Issue Date:** 6/1/16

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<tr>
<td><strong>G. SAFETY MEASUREMENTS</strong></td>
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<tr>
<td>11.</td>
<td>State the safety parameters.</td>
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<td>Define Protocol Deviations, AEs, SAEs, and UPs; Discuss expected AEs from previous experience with the investigational product; Discuss possible anticipated AEs; Indicate time points for review of the study progress, AEs, and SAEs; State how safety information will be assessed, recorded, analyzed and reported; State the criteria for assessing seriousness and relationship to product, ultimately the PI’s responsibility; Indicate the reporting procedures and timeframes for AEs (expected and unexpected), include 24 hour contact information for telephone and/or fax reporting.</td>
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<td>12.</td>
<td>Develop the Data Safety Monitoring Plan (DSMP)</td>
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<td>DSMP is required for all research studies involving greater than minimal risk to human subjects.</td>
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<tr>
<td><strong>H. EFFICACY MEASUREMENTS/DATA ANALYSIS</strong></td>
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<tr>
<td>1.</td>
<td>Discuss how data will be analyzed. Indicate the statistical methods to be used.</td>
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<td>Discuss the details of the statistical approach to be followed in the study including: sample size: how the sample size was determined and the assumptions made in making this determination; efficacy endpoints: group as primary endpoints, secondary endpoints, and safety endpoints (these should also be defined before the study begins); the selection of subjects to be included in the analyses (e.g. all randomized subjects, etc.); details of how the results will be analyzed and reported; specifically:</td>
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<tr>
<td><strong>I. QUALITY ASSURANCE MEASURES</strong></td>
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<td><strong>13.</strong> Discuss how the trial will be monitored.</td>
<td>Describe monitoring policies and procedures, including: on-site monitoring; specify frequency and who is expected to perform the visits.</td>
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<td><strong>14.</strong> Provide explanation of internal or external audits.</td>
<td>Explain auditing of the study files and source documentation to verify data accuracy. The protocol (or other written agreement) specifies that research centers will permit direct access to source data/documents for trial-related monitoring, audits, review, and inspections.</td>
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<tr>
<td><strong>J. ETHICS</strong></td>
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<td><strong>15.</strong> HIC/IRB</td>
<td>The U.S. Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) regulations require all human subject research be reviewed and approved by an IRB prior to beginning the study.</td>
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<td><strong>16.</strong> Informed consent</td>
<td>State that informed consent will be obtained in compliance with FDA regulations, HHS regulations, ICH Guidelines for GCP, etc. Cited documents may be included as appendices in the protocol. Confidentiality issues and ownership of data and tissue samples should also be addressed if relevant.</td>
</tr>
<tr>
<td><strong>17.</strong> Protection of Human Subjects</td>
<td>Include a statement that the trial will be conducted in compliance with the protocol, if relevant.</td>
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</tbody>
</table>
**K. DATA MANAGEMENT**

Determine the data management tools for the study, including CRFs and source documents; Explain record retention.

**L. INVESTIGATOR STATEMENT**

Signatures of the PI and sub-investigators indicate agreement that the protocol contains all the necessary information to conduct the study, and affirm that the site will comply with the protocol, GCP guidelines and applicable regulatory requirements, and will not begin the study until IRB and other regulatory approvals have been obtained.

**M. PUBLICATION POLICY** (if not addressed in a separate agreement)

Detail how data will be presented, who can or cannot write up the results of the study and how details of authorship will be determined.

**N. REFERENCES**


**O. APPENDICES**

Include any other documents referenced in the clinical protocol. The appendix may include:
- the informed consent form
- CRF and other data collection forms

**Competed by:**

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**Reviewed by:**

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