



Research Education Improvement Program  
(REIP)  
Connecticut Children's Medical Center  
Program Manual for PI's and Study Staff

Connecticut Children's Medical Center  
Research Compliance Program  
80 Jefferson St  
Hartford CT

Phone 860-545-8376

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## I. INTRODUCTION

The purpose of the Research Education Improvement Program (REIP) is to provide support, information, and education to ensure that studies are being conducted in compliance with federal, local, and protocol guidelines. The program is designed to be proactive and integrative to prevent problems before they happen without impairing research.

The REIP is founded upon the following key areas:

**Education and Collaboration:** to provide guidance and education regarding local and federal regulations that govern the conduction of a research study, improve identified deficiencies and promote strengths through a collaborative and educational effort among REIP, Principal Investigator and research staff members.

**Review of research trials:** to implement a system that will ensure compliance and identify problems and/or potential areas of non-compliance. Also, to provide education to the Principal Investigator and the research staff.

**Corrective action plans:** to help Principal Investigators and/or the research staff devise and implement a corrective action that will address deficiencies noted in a review report.

The program will be structure to examine current policies and practices to determine what works, what needs improvement and what needs to be developed to facilitate a safe, positive and constructive research compliance process.

The procedures are subject to change when deemed necessary and beneficial, as the program is dynamic and open to continuous feedback from the research community.

## II. PROGRAM OVERVIEW

The REIP was established in compliance with federal and local regulations. This review manual has been developed to help Principal Investigators and their research staff understand all aspects of the review process.

### **Roles and Responsibilities of the REIP:**

#### **Research Review Monitor:**

- Create and incorporate standards and guidelines that help Principal Investigators and research staff with research compliance activities.
- Facilitate research compliance initiatives.
- Provide education for investigators, clinical coordinators, and other research-related staff concerning federal and local requirements in regards to conducting research studies.
- Routinely review research studies to assess research compliance, data quality, and identify potential noncompliance issues.
- Provide guidance for improvement of areas that are identified as deficient.
- Develop a process for formulating and recommending corrective action plans to address instances of deficiencies.
- Act as the liaison between the Principal Investigators, IRB, and the Research Compliance Committee.

**REIP Chair:**

- Assist in the assessment of the research review findings presented by the RRM.

**Institutional Review Board:**

- Provide IRB documents needed for research review.
- Assist in addressing review findings (e.g., serious or continuous non-compliance).

**Institutional Officer:**

- Assist in addressing events related to Principal Investigator failure to submit corrective action plans.

**Research Compliance Committee:**

- Consists of members representing various research disciplines.
- Meet on a monthly basis.
- Identify research non-compliance risks and prioritize actions in the areas given priority.
- Recommend educational sessions for the research community regarding potential areas of risk.
- Recommend policies.

**Principal Investigator:**

- Ensure that all the relevant materials are available for the review.
- Be available at the beginning of the review and for the post-review findings discussion.
- Ensure that the study staff is available to assist during the review.
- Create and implement a corrective action plan if needed.

**Types of Reviews To Be Conducted****Random/Scheduled Reviews:**

This review is considered a full review. Focus of the review includes roles and responsibilities of research team members, regulatory and IRB compliance, consent form elements, consenting process, subject recruitment, eligibility, patient case review for protocol adherence, source documentation and data collection, adverse events, file security, pharmacy operations and other suitable aspects of the study. Reviews may also be randomly selected at the time of continuing review to verify from sources other than the researcher that no unapproved changes have occurred since previous IRB review.

**Informed Consent Reviews:**

This review is intended to ensure that adequate informed consent and HIPAA Authorization are provided to study participants. This type of review may include observation (when possible) of the consenting process; verification that the person consenting potential study participants is qualified and designated by PI; review of the consent form and HIPAA Authorization for a valid IRB date, appropriately signed and dated by the participant/parent/legal guardian; documentation of consent process; confirmation that a copy was given to subject; and review of the consent form for basic elements of consent according to federal regulations.

**For Cause Reviews:**

This review is conducted when concerns regarding compliance, protocol adherence, or study participant safety are brought to the attention of the IRB, Department of Research Operations, Risk Management, Research Review Monitor (RRM), or the Corporate Compliance Officer. This is considered a full review of all the regulatory and study participant's documents for compliance.

### **Re-reviews for Review Findings Requiring a Corrective Action Plan:**

This review is conducted when a corrective action plan has been put into place to correct deficiencies noted during the research review. These reviews will be conducted within 6 months of the research review date. The purpose of these reviews is to ensure that the corrective action plan is being followed by the Principal Investigator and/or research staff. The re-reviews will be conducted in the same manner as a full random research review.

## **III. THE RESEARCH EDUCATION IMPROVEMENT PROCESS**

### **Educational Sessions**

The goal of these sessions is to educate the research community of the program's purpose and overview of the research review process. During these educational sessions, feedback will be obtained from the research community regarding what they need and would like to see incorporated into REIP.

The RRM will conduct several educational sessions to ensure that everyone who conducts clinical trials will be able to attend.

The periodic educational sessions will start as reviews are completed. Information regarding the review process and findings will be assessed to identify areas that need improvement and provide applicable educational sessions. The intention of these educational sessions is to re-emphasize the purpose of the program, provide updates on the program's progress, and provide education based on areas of deficiencies identified through the reviews.. These sessions will allot equal time for the research community to offer ideas, opinions, responses to the program's progress and results.

All principal investigators and research staff members will be invited to attend through email notification at least 1 month prior to the session. Reminders will be sent the week and day before the session.

### **Research Review Process**

#### **Selection of the Study**

The Research Review Monitor (RRM) will randomly choose a study from a list generated from the REIP database. The random choice of studies will be conducted by creating a query as to the Principal Investigator, department, and if the study has not been reviewed to date. This query system will decrease the likelihood that a department and/or Principal Investigator will be selected twice consecutively. Research reviews will initially focus on Principal Investigator initiated studies since typically these studies are not monitored for compliance. Depending on the number of studies listed on the report, every 5 to 10 studies listed will be chosen for review.

Once the study is chosen the RRM and/or designee will contact the Principal Investigator to verify that patients have been enrolled and if so, such patients are receiving the treatment/study procedure or intervention.

If patients have not been enrolled in the study it will be put back into the database for a future review selection.

## **Scheduling the Review**

The review dates will be scheduled according to the type of review to be conducted. Below is the timeline for each type of review:

- Random Scheduled and Informed Consent reviews: The review date will be scheduled 4-6 weeks in advance.
- “For cause” review: The review date will be scheduled 24 to 48 hours in advance. If there are serious concerns about patient safety there may be minimal notification.

## **Pre-Review Processes**

### **Random Scheduled Review:**

Within one or two days of a study being selected for a review, the Principal Investigator and/or the study coordinator will receive a Research Review Intake Form to complete. The following information will be requested:

1. Is the study open or closed for enrollment
2. The number of patients enrolled
3. A list of participants enrolled in the study and their study status
4. A list of co-investigators and study staff
5. The role of the study staff listed
6. The number of amendments, if applicable
7. Whether there is an investigational drug or device being used
8. What dates the Principal Investigator and study staff will be available for an review

The form should be returned to the REIP Office within one (1) week of receipt to allow sufficient time to select the date and cases for the review.

### **Informed Consent Review:**

Within one or two days of a study being selected for a review, the Principal Investigator and/or the study coordinator will receive a Research Review Intake Form (as noted above for Random Scheduled Review).

The form should be completed and returned within one (1) week of receipt to allow sufficient time to select the date and cases for the review.

When the informed consent process is going to be observed the RRM will work with the Principal Investigator or study staff to devise a system to inform the RRM when a potential new participant will be consented.

### **For Cause Review:**

The RRM will call the Principal Investigator and the study staff notifying them that a “For Cause” review will be conducted in the next 24-48 hours. At that time they are asked to send the Research Compliance Monitor a list of study participants, either by fax or e-mail.

## **Selection of Study Participant Cases**

During a study review, all subjects enrolled in the study will be assessed for consent and eligibility compliance. Detailed reviews, based on review type, will be done on subjects according to the following criteria:

1. General selection:
  - i. If total enrollment is **3 or less**, all subjects will be reviewed.

- ii. If total enrollment is **between 4 and 14**, 3 subjects will be randomly selected.
  - iii. If total enrollment is **15 or more**, ~10% of the subjects will be randomly selected.
2. Random selection: If total enrollment is 4 or more, all study participant's IDs will be entered into a database and use the random selection option based on criterion (a)(ii – iii).
  3. The selected study participants' IDs will be entered into the Research database to ensure that participant's are not selected twice for a review.

### **Notification of the Research Review Date and Study Participant Cases**

Once the date and cases are selected, the Principal Investigator and study staff will receive a letter at least three (3) weeks prior to the review. The letter will include a list of cases selected for review. This will allow the study staff sufficient time to request the medical records and prepare for the review.

### **How to Prepare for a Research Review**

The PI and/or study staff should book a room for the day. If applicable, contact the pharmacy and any other departments involved in the conduction of the study to inform them of the research review and the date.

The Principal Investigator is responsible for ensuring that all relevant materials are available for the review. Such materials include: in-patient and outpatient medical record, research record, Regulatory File, IRB file, informed consent documents, and other study related information.

For the Informed Consent review, the medical records and research record is all that is needed. If time allows the consent form, HIPAA Authorization, and documentation of the consent process should be flagged.

To facilitate the review process, it is recommended that the study staff flag\* all source documents such as hospital/clinic records, research notes, eligibility information, imaging studies, consent forms, etc, that pertain to the study. These documents will be checked against the data noted on the data collection forms or what is used to collect the data. The RRM will provide guidance on how to prepare the documents for the review (see attachment A).

\*The reason for asking the appropriate documents to be flagged is for easy access to the required documents, which helps facilitate the review and contributes to less questions and asking for documentation by the RRM.

The medical records generally contain major source documents for all the information that is abstracted onto data collection forms. There may be other sources, such as clinic charts, computer lab records, or "shadow charts." These patient records can be used as source documents, as long as they are signed and dated on a real-time basis.

Various verbal reports (from lab or radiology, for example) are acceptable source documents if they are summarized, signed, and dated.

If a study participant was referred from other physician's offices and/or hospitals, efforts should be made to obtain those records ahead of time. If they cannot be obtained a note should be written that the information cannot be obtained or is missing prior to the research review.

## IV. CONDUCTING THE RESEARCH REVIEW

### **Interview**

The day of the review, a half an hour interview with the Principal Investigator will be conducted prior to the review starting. The interview will allow the PI to provide the RRM with an overview of the study and how it is conducted.

### **Review of Source Documents**

During the review, the RRM will examine specific data related to the conduct of the study according to the protocol and regulatory requirements as described in this section. Source documents are used to independently verify study data and for protocol compliance. Source documents may include, but are not limited to, the following:

- Inpatient and outpatient medical records
- Research record
- Progress notes
- Diagnostic reports (x-rays, scans, ECGs, etc.)
- Laboratory data
- Study flow sheets and other research records
- Subject diaries/calendars
- Informed consents, HIPAA Authorizations and IRB documents
- Correspondence if applicable
- Staff authorization logs and/or research review intake form
- If applicable the following documents will be reviewed for accuracy and proper maintenance:
  - FDA documents
  - Investigational brochure or drug inserts
  - Lab certificates and lab normals
  - All investigator's CVs and licenses
  - Compensation for study participation
  - Billing procedures for study procedures
  - Data Safety Monitoring Plan

### **Review of IRB Documentation**

The both Principal Investigator and IRB Department files will be reviewed for the following documentation:

- Initial IRB approval
- IRB annual re-approval
- IRB approvals prior to patients starting the study
- IRB approval of all amendments
- Approved advertisements and/or recruitment material
- Documentation that all adverse events were reported correctly and in a timely manner
- Documentation that protocol deviations have been reported
- Verify that both the IRB approved protocols and the protocols in the Principal Investigator file match
- IRB meeting minutes

### **Review of the Regulatory File, if applicable**

The Regulatory file will be reviewed for the following documentation:

- Currently approved protocol
- Currently approved consent forms and HIPPA authorization

- Conflict of Interest forms
- Financial Disclosure forms
- Correspondence
- Safety reports and/or serious adverse events
- List of the IRB members
- Principal investigator and co-investigators' CVs
- Investigator Brochure or drug package insert
- Information regarding the device
- FDA 1572
- FDA 1571 along with the IND application, annual report and correspondence
- Lab normals, lab manager's CV, and lab certificates

### **Review of Pharmacy Operations, if Applicable**

The following are guidelines for assessing compliance with drug accountability:

- Research drug was dispensed.
- The drug logs are adequately maintained and completed.
- The drug count matches the drug logs.
- The investigational drug is properly stored and secured.
- The investigational drug has not expired.

### **Review of Device Accountability Forms and Devices, if Applicable**

The following are guidelines for assessing compliance with device accountability:

- The device accountability forms are correctly filled out and maintained.
- The device count matches the accountability form.
- The device (ices) is properly stored and secured.
- The device (ices) has not expired.

### **Review of Study Participants Medical and/or Research Records**

The following are guidelines for assessing compliance for data quality and protocol compliance:

- Informed consent and HIPAA Authorization are checked for the following:
  - Signed and dated
  - Proper consent form and HIPAA Authorization were used
  - Assent is signed and dated, if applicable
- Eligible criteria for enrollment into the study
- Study-related procedures / events were done according to the protocol
- Adverse events related to treatment were reported properly
- General quality of the data collected (data collection forms are checked against documents)
- If applicable the following will be reviewed:
  - The treatment was given as indicated in the protocol
  - Evaluation of disease outcome response
  - Storage of research records and databases
  - Patient reimbursements
  - Billing procedures for research related procedures

### **Research Review Findings**

#### **Definitions of Deficiencies**

Below are the standard definitions used to describe compliance deficiencies for each item assessed for the review (i.e. consent form, treatment given, and pharmacy stored drug properly):

- **Potentially Serious or Continuing Non-Compliant Deficiencies:**  
A potentially serious or continuing non-compliant deficiency is defined as a variance from protocol-specified procedures or Good Clinical Practice that threatens a patient’s rights or safety. A Continuing Non-compliant deficiency is a pattern of non-compliance that indicates an unwillingness to comply or a lack of knowledge that may lead to an adverse effect on the rights and welfare of participants or may place participants at an increased risk of harm.
- **Lesser Deficiencies:**  
A lesser deficiency is a minor variance from the protocol-specified procedures or Good Clinical Practice that that neither threatens a patient’s rights nor their safety.

### **Assigning Levels to Research Review Findings**

The components of the research review (i.e. regulatory, IRB, patient case review) will independently be assigned an assessment of either **Acceptable; Acceptable Needs Follow-up, or Potentially serious or continuing non-compliant deficiencies;** based on findings at the time of the review.

The Principal Investigator and/or research staff will be encourage to correct any **misunderstandings** and/or supply missing documentation to the RRM during the review. However, if documentation is not available at the time of the review they will be asked to send it to the RRM as soon as possible.

Below are the definitions that will be used to assess the components of the review:

#### **Acceptable**

- No deficiencies identified
- Lesser deficiencies identified that were corrected during the review

#### **Acceptable Needs Follow-up**

- Lesser deficiencies identified during the review but could not be corrected during the review
- Missing documentation that needs to be sent to the RRM because it was not available at the time of the review

#### **Potentially Serious or Continuing Non-Compliant Deficiencies**

- Potentially serious or continuing non-compliant deficiencies identified
- Major flagrant deficiency (ies) found
- Patient safety is being compromised

#### **The Post Research Review Meeting**

The RRM will meet with the Principal Investigator and/or research staff at the end of the review to discuss the findings and any issues that are addressed that day will be not be reflected in the report. Any findings that are potentially serious or continuing non-compliant will be discussed with the REIP chair within 24 hours of the research review.

## **V. REPORT OF RESEARCH REVIEW FINDINGS AND FOLLOW UP**

### **Review Report Findings**

*Effective July 2007, the following is an interim plan that will be followed until the Director of Human Protections is approved and hired.*

The RRM and REIP chair and/or designee will review the Preliminary Findings Report along with additional documentation and/or corrective action within 1-2 weeks of completing the review. However, any potentially serious or continuing non-compliant findings noted by the RRM will be communicated to the REIP chair and IRB Chair/Director within 24 hours of the review to review the findings.

### **Acceptable Review Findings**

If the review is rated as **Acceptable** the Principal Investigator will be notified by letter of the findings.

### **Acceptable Needs Follow-up Findings**

If the review is rated as **Acceptable Needs Follow-up** the steps below will need to be followed:

- If there is outstanding documentation that is needed the Principal Investigator will be given two weeks from the time of the review to send all the requested documentation to the RRM.
- The RRM and REIP chair and/or designee will review the findings along with the documentation. If the documentation and review findings are considered acceptable a letter will be sent to the Principal Investigator.
- If after the review additional information is needed the following steps need to be done:
  - The RRM will contact the Principal Investigator to obtain the additional information needed.
  - Once the information is obtained will forward the information to the REIP chair. If the REIP Chair approves the preliminary report the RRM will send the Final Principal Investigator Response Form to the Principal Investigator.
  - The Final Response Form will also include room to develop a corrective action plan, if needed.
  - The Principal Investigator has 2-3 weeks to complete the final Principal Investigator Response Form and return it to the REIP office.
- The Form is then filed accordingly in the REIP Office.
- The re-review will be conducted 6 months after the research review date to ensure that the Principal Investigator and/or study staff is following the approved corrective action plan.

### **Review Findings for Other Departments Involved in the Conduct of the Study**

If deficiencies are noted in Pharmacy, IRB, Radiology, etc., the same review process will be followed that is mentioned above.

### **Potentially Serious or Continuing Non-compliant Deficiencies Review Findings**

If the review findings are considered **Potentially Serious or Continuing Non-compliant Deficiencies**, the steps below will need to be followed (refer to the IRB's policy for Potentially Serious or Non-compliance Issues):

- The RRM will contact the REIP Chair and IRB chair within 24 hours. The preliminary findings will be reviewed by the IRB chair, RRM, and interim REIP chair.
- If the review findings are not considered serious and or continuing non-compliant recommendations will be sent to the Principal Investigator. The Principal Investigator will have one (1) week to submit a corrective action plan to the IRB Chair and REIP Chair.
- If the review findings are still considered to be potentially serious and continuing non-compliant the findings will be reviewed according to the IRB's policy and procedures concerning non-compliant reporting and investigations

### **Failure To Submit a Corrective Action Plan**

If the Principal Investigator fails to provide a corrective action plan for components rated as Acceptable Needs Follow-up within the required time frame, the following procedures will be done:

- A written notice is sent to the Principal Investigator that the response form is overdue and a five working day grace period will be granted for the submission of the response form.
- If a response form is not received by the RRM during the five (5) day grace period, the IO will be notified for further actions.

If the Principal Investigator fails to provide a corrective action plan for components rated as Potentially Serious or Continuing Non-compliant Deficiencies within the required time frame, the following procedures will be done:

- A written notice is sent to the Principal Investigator that the response form is overdue and a five (5) working day grace period will be granted for the submission of the response form.
- If a response form is not received by the RRM during the five day grace period, the chair of the RCC, IRB chair, and IO will be notified for further actions.

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References:

1. Clinical Trials Monitoring Branch Cancer Therapy Evaluation Branch Division of Cancer Treatment and Diagnosis National Cancer Institute: Guidelines for Monitoring of Clinical Trials for Cooperative Groups, CCOP Research Bases, and the Clinical Trials Support Unit (CTSU)
2. Children's Oncology Group Audit Manual
3. Clinical Trials Administrator July 2007, Vo. 5 No. 7: "Institution starts monitoring service for in-house protocols"
4. Clinical Trials Administrator July 2007, Vo. 5 No. 7: "University of Minnesota's Clinical Trial monitoring plan"
5. University of Minnesota's Website for Regulatory Affairs
6. University of Alabama's Office of Research Compliance Website.
7. Vanderbilt University Institutional Review Board's Compliance Program for the Protection of Human Research Participants.
8. Columbus Children's Hospital Website of Research Compliance and Integrity.
9. FDA and ICH Good Clinical Practice Guidelines
10. Children's Hospital of Boston

APPENDIX A

**CHECKLIST FOR CHART PREPERATION FOR THE RESEARCH REVIEW**

*Have you flagged the following information in the medical record (s) and/or research chart:*

	The study consent (s) and HIPPA forms
	Source documentation needed to ensure the patient’s eligibility (i.e. physician notes, labs, scans, other information or procedures needed for the protocol
	Flowsheets used to document when an investigational agent and/or device were used.
	Source documentation needed for each study visit
	If applicable, medication sheets
	If applicable documentation of how a questionnaire was administered
	If applicable, any correspondence with the sponsor regarding the patient
	If applicable, all the information associated with a serious adverse event
	If applicable, patient diaries or calendars
	Have you labeled the flag with the information that the flag is associated with? For example, the flag label reads “Study Consent”, “Eligibility Information”.

If you have any questions please feel free to call Kim D. Jennings at 545-8376.