ORIENTATION FOR NEW CLINICAL RESEARCH PERSONNEL

MODULE 2

Presented by

NC TraCS Institute
UNC Office of Clinical Trials
UNC Network for Research Professionals
Overall Agenda for Orientation

• **Module 1:**
  Introduction to Clinical Research, Education, and IRB

• **Module 2:**
  Study Start-up and Roles of Research Personnel, Study Documentation and GCP, Informed Consent

• **Module 3:**
  Contracting, ClinicalTrials.gov, IDS / Device Policy, Essential Documents

• **Module 4:**
  Recruitment, Preparing Industry and NIH Grant Budgets, Accounting, and Billing Coverage Analysis

• **Module 5:**
  COI, From CDA to Study Close Out
STUDY TEAM RESPONSIBILITIES

Laura Tuttle, MA, CCRP
Assistant Director, Hypertension Research Program
Research Teams

Principal Investigator

Sub-Investigators / Co-Investigators

Study Coordinators

Data Managers

Regulatory Coordinators
Principal Investigator

Oversight of Study Conduct

- Science
- Integrity & Ethical Conduct
- Business Operations
- Protocol Compliance
- Team Training
- Participant Rights & Safety
PI Responsibilities from FDA 1572

FDA 1572 is a legally binding document, in which the PI agrees to:

1. Conduct study in accordance with protocol
2. Personally conduct or supervise the study
3. Ensure proper informed consent is obtained
4. Report adverse events
5. Ensure all members of study team understand responsibilities
6. Maintain adequate and accurate records
7. Maintain compliance with IRB
8. Comply with all FDA regulations (21 CFR 312)
“I agree to personally conduct or supervise the described investigation(s).”
Investigator Obligation *With or Without* FDA Involvement

- Obtain IRB approval before performing the protocol and before instating any protocol changes

- Perform the protocol as approved by the IRB

- Provide the IRB with accurate and complete information and updates as the information changes

- Notify the IRB of all unanticipated or serious adverse events involving risk to human subjects

- Provide all reports required by the IRB on the timeline required by the IRB
Study Coordinator

- Research Assistant
- Research Associate
- Research Nurse
- Project Manager
- Research Manager
Primary Responsibility

Per UNC, the role of a study coordinator is to “... ensure smooth, accurate progress of the project from the planning stage through study end (and often beyond) by acting as liaison to the investigator, the subject, the institution, and the company or government sponsor.”
Primary Responsibility

- The Invisible Hand in Clinical Research: The study coordinator’s critical role in human subjects protection (Davis et al., 2002)
  - Metaphors for 3 primary roles:
    - Mother – patient welfare / patient advocate
    - Lawyer – participant rights and welfare / providing neutral information
    - Teacher / Policeman – understand value of protocol and defend it

- Conducting Clinical Research, Judy Stone, MD
  - Coordinators manage the logistics of everything!!!
Shared Responsibilities

Many PI responsibilities are delegated and become the coordinator’s operational responsibility.

- Know what responsibilities belong only to PI and what roles you are capable of performing

FDA Guidance Document: Investigator Responsibilities – protecting the rights, safety, and welfare of study subjects

General CRC Responsibilities: Protocol Evaluation

- Subject availability
- Personnel requirement
- Equipment & facility availability
- Testing capabilities
- Develop timelines
- Propose & negotiate alternatives to improve implementation
General CRC Responsibilities: Administrative

- Interact with IRB, lab staff, clinic staff, pharmacy, study sites, etc.
- Prepare IRB documents including ICF
- Prepare study budget
- Ensure all documentation is maintained
- Interact with sponsor
- Interact with PI’s and sub-investigators
- Coordinate and participate in monitoring visits with sponsor
- Complete CRFs and submit to sponsor
- Facilitate inspections/audits
- Document study progress
General CRC Responsibilities: Study Subjects

- Recruit participants
- Determine eligibility
- Discuss study with subject
- Obtain informed consent
- Schedule study visits
- Ensure all study tests and visits are done at appropriate time intervals
General CRC Responsibilities:
Study Subjects

• Monitor laboratory data and clinical signs for potential adverse events (and report to PI)

• Adverse Events (AEs)
  • Assist PI with gathering information to help PI determine classification, and causality
  • Observe and document AE’s
  • Act on PI’s recommendation
  • Maintain follow-up until reconciliation
  • Communication with sponsor
General CRC Responsibilities: Study Subjects

- Provide information for treatment and reactions
- Administer or dispense investigational agent, as outlined in the protocol, under the investigator’s supervision
- Promote subject compliance by providing patient support and education
- Arrange for study subject compensation
General CRC Responsibilities: Data Management

- Investigational Drug Accountability
  - Order, store, dispense, retrieve, log
  - Randomization codes
  - Unblinding procedures
- Prepare lab specimens; ship biological samples and radiologic films
- Ensure data is collected in accordance with the protocol
- Complete data collection forms
- Enter data into database
- Maintain data security
- Check data for validity
- Respond to data queries
CRC: Rewards!

- Expand your knowledge!
- Positively affect participants!
- See the impact of your work!
- Work with diverse groups of people!
- Be a vital part of interesting, exciting work!
- Produce science that will shape our future!
STUDY START-UP AND IMPLEMENTATION

Laura Tuttle, MA, CCRP
Assistant Director, Hypertension Research Program
"Strength and speed are useful, son, but coordination is crucial!"
Protocol Implementation

Before your study starts, some things to consider:
• Study start up meeting
• Team training (and documentation)
• Notify providers, nurses, clinic staff, etc. of upcoming research protocol
• Recruitment plan and materials
• Source documents
• Tracking logs
• Data management plan
• Organization of study materials
Protocol Implementation

Organization of study materials:

- Regulatory binder
- Randomization information
- Supply order forms
- Investigational drug
- Standard operating procedures (SOP’s)
- Case report forms (CRF’s)
- Visit checklists
Protocol Implementation

Creation of source documents:

- Review your study visit schedule
- Review the case report forms to ensure you collect all information that will be documented on CRF
- Develop standard forms for department that can be used across studies
  - Physical exam form
  - Medical history form
  - General research record
  - Documentation of Informed Consent Template
Depending on study, development of a study start up checklist may be helpful.
... AND THIS IS THE FORM YOU SEND BACK TO CONFIRM YOU'VE SENT BACK ALL THE OTHER FORMS!
GOOD CLINICAL PRACTICE & STUDY DOCUMENTATION

Juanita Cuffee, BA, MPH
Clinical Research Associate; Pediatrics, Hematology/Oncology
Chair, NRP
E6 Good Clinical Practice: Consolidated Guidance

• 1996: In an attempt to provide consistency among clinical trials, US, European Union, and Japan established a unified standard, called the International Conference on Harmonisation’s “Good Clinical Practice: Consolidated Guideline,” (ICH-GCP).

• Objective of “guidance is to provide a unified standard to facilitate mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.”

• E6 Good Clinical Practice: Consolidated Guidance recognized by industry sponsors as the gold standard for conduct of ethically and scientifically sound human subject research.

From the Introduction of Guidance for Industry, E6 Good Clinical Practice
<table>
<thead>
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<th>Describes:</th>
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| • Qualification of an investigator  
• Education and training of study staff  
• Delegation of study-related tasks  
• Requirement for IRB review  
• Compliance with the protocol  
• Responsibility for investigational product accountability  
• **Informed consent**  
• Safety reporting  
• **Trial management & record keeping**  
• **Data quality** and integrity, quality control  
• **Essential documents** for a trial |
Why is Adherence to GCP Important?

Main tenets of GCP: research involves good science, is verifiable, monitored, well-documented, and study complies with the highest ethical standards.

Adherence to GCPs:
• Protect the rights and well-being of human subjects
• Ensure accuracy and credibility of the data and reported results
• Ensure conduct of the trial is in compliance with:
  • the protocol/amendment(s) currently approved by the IRB
  • applicable regulatory requirements
  • institutional policies
  • all applicable rules and regulations
Who Should Adhere to GCP?

• The general concept of GCP is essential for any research study involving human subjects.

• Whether conducting research involving a new drug or device, a behavioral intervention, or an interview/survey, Good Clinical Practice (GCP) provides investigators and study teams with the tools to protect human subjects and collect quality data.

• Following the ICH-GCP is one of the best ways to substantiate the quality of any research study and its resulting data.
GCP Basics

• The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial related duties and functions – 4.2.4

• Application:
  • Documentation of protocol training for the original protocol and each protocol amendment by ALL study staff.
  • Documentation of receipt and understanding of the Investigator Brochure (IB) by PI and/or Sub-Investigators.
  • Documentation can be wet ink or electronic
  • Consider using a learning management system
GCP Basics

• During and following a subject’s participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware. – 4.3.2

• Application:
  • In the event of a clinically significant laboratory value related to the study drug or device, the PI/Sub-I should ensure that care is sought (and documented).
  • Tip: The IRB will want to know what medical resources are available for subjects on a clinical trial.
GCP Basics

• The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment except where necessary to eliminate an immediate hazard(s) to the trial subjects, or when the change(s) involve only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)) – 4.5.2

• Application:
  • Sponsor approved deviations should be reviewed by the IRB prior to implementation especially those affecting eligibility, dosing etc.
Documentation

• Once a scientifically valid research idea has been proposed and approved, the key to successful implementation of the study lies in the documentation.

• “If you didn’t document it, it didn’t happen.”

• Validity of research data rests in the documentation.

• Resources, such as checklists and templates assist investigators & study staff in implementing, and documenting that they followed GCP and the protocol.
Source Documents

- **Source Documents**: All information in *original* records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial *necessary for the reconstruction and evaluation* of the trial.

  International Conference on Harmonization E6

- The first place something is recorded is considered the **source document** for that clinical trial activity.

- A “trail for the trial”: Source documents should create a “trail” so that **anyone** can verify and follow what happened throughout a clinical trial and where the data came from (an audit trail).
Types of Source Documents

- Medical history
- Hospital records
- Clinic & office charts
- Progress notes
- Lab notes
- Memoranda
- Meeting minutes
- Notes to file
- Phone records

- Subject diaries
- Questionnaires
- Subject files or records
- Drug dispensing records
- Recorded data from automated instruments (DynaMap, ECG, EEG, )
- X-rays, scans, MRIs
Example of a source document?

Subject
105-0001 ABC
3/1/06

9 AM
142/80, 76, 18,
36 °C
ALCOA* for Data Quality

- **Attributable:** is it obvious who wrote it?
- **Legible:** can it be read?
- **Contemporaneous:** is the information current and in the correct time frame?
- **Original:** is it a copy; has it been altered?
- **Accurate:** are conflicting data recorded elsewhere?

*Stan W. Woolen, 1999 DIA Meeting*
Important Events to Document

- The Consent Process (more than just signed consent form)
- Documentation of subject eligibility (inclusion/exclusion criteria)
- Study randomization, study drug adherence or non-adherence
- Completion of all protocol-required tests, procedures
- Missed visits, subject contacts, procedures, or examinations
- Protocol deviations & violations (notifications to IRB / sponsor and corrective actions)
- All subject contact – either via phone or in person (include date/time and reason for contact)
- Unanticipated problems or adverse effects and relationship to study intervention, severity, action taken and reporting to IRB
- Subject termination (withdraw of consent, lost to follow up, PI removal)
Documentation of AEs and UPs

- Keep log of AEs, SAEs, Unanticipated Problems
- Track adverse events from time consent is signed, until resolution of any serious events - even after the study period ends.
- Be consistent with terminology and descriptions.
- Use a severity scale in evaluating adverse events (CTCAE scale or mild, moderate, severe scale) and document according to scale

- Decisions regarding AE reporting and management are the responsibility of the PI so keep them in the loop and encourage documentation.
- The PI has the final decision on causality, severity and relationship of adverse events
Templates *Improve* Source Documentation

- Some research data collected on Hospital based forms as part of medical care:
  - Vital signs on clinic record sheet
  - Medication administration on MAR for inpatients,
  - Laboratory tests
  - History and physical exam
- Other research data only collected by study staff and not maintained in Medical Record or on any other form.
  - Use of templates to document research data helps study team collect required data and have a place to record it.
- Other data can be written on progress notes.
Eligibility Criteria

• IRB approval of protocol includes approval of inclusion & exclusion criteria as written. These eligibility criteria are NOT guidelines, but are requirements that must be followed.

• The “inclusion/exclusion criteria” define the study population, and ensure the safety and the integrity of the data

• Investigator may wish to enroll a subject who does not precisely fit the eligibility criteria
  • PI must obtain IRB approval for the change in eligibility criteria
  • May make an exception for a single subject (not change criteria in protocol)
  • After the amendment or exception is approved by IRB, the subject can be then be enrolled
I / E Criteria Checklists

- Good practice for study teams to incorporate an eligibility checklist into each subject’s study record so that study staff can document on a form how each of the inclusion and exclusion criteria have been met.
- Create a template that is study specific, listing all the inclusion and exclusion criteria for the study and check off that subject meets each and every criteria

Documentation of Eligibility Important!

- Keep supporting documentation that demonstrates that subject meets criteria (e.g., colonoscopy results to demonstrate normal colon)
Sample Inclusion/Exclusion Criteria Checklist

**SUBJECT ID:** ________________  **SCREENING VISIT**

### Inclusion/Exclusion Criteria:

<table>
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<tr>
<th>Date of Visit</th>
<th>mm</th>
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### SECTION I: INCLUSION CRITERIA

1. Patient is between 18 and 65 years old
2. Patient’s BMI is between 18 and 30 kg/m²
3. Patient is in good general health
4. Patient has agreed to fast 8 hours and not consume alcohol 48 hours prior to PK sampling days
5. Patient is able and willing to provide informed consent

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<td>4.</td>
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<td>5.</td>
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### SECTION II: EXCLUSION CRITERIA

6. History of any pancreatic or biliary disease (e.g., Familial colorectal cancer syndromes, Ulcerative colitis or Crohn's disease)
7. History of any acute or chronic illness that requires current medical therapy, including active gastrointestinal conditions, that might interfere with drug absorption
8. History of large bowel resection for any reason
9. Diagnosed narcotic or alcohol dependence
10. Woman of childbearing potential who does not agree to practice effective birth control
11. Use of curcumin within the last 14 days
12. Allergy to curcumin
13. Individual with creatinine, AST or ALT above 1.5 times the upper limit of normal at baseline
14. Personal or inherited bleeding disorders or therapeutic anticoagulation with warfarin

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<th>Criteria</th>
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<td>14.</td>
<td>Yes</td>
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</table>
If the responses to all the inclusion criteria are YES and all the exclusion criteria are NO, the subject is eligible to participate in the trial.

Is the subject eligible to participate in the trial? YES NO

If NO, discontinue the subject and complete the study termination form.

If YES, I have reviewed the inclusion and exclusion criteria and have determined that the subject is eligible for participation in the trial.

Investigator ___________________________ Date ___________
Case Report Forms (CRFs)

- CRFs are **paper** or **electronic** documents/forms designed to record all information required by the study protocol for a participant (provided by Sponsors).
- **All information entered on CRF must be supported by source documents**
- If data recorded directly on CRF, there should be an entry in subject's medical record or subject file that records date information was obtained, how and by whom.
- CRFs may be used as a source document **IF** data elements are newly created and not transcribed from other sources.
- FDA opinion that copies of CRF used as a source document are not a replacement for original source documentation.
Helpful Hints for Source Documentation

- Mistakes and mishaps occur, visits, contacts and tests may be missed, subject might not tell you about an adverse event or problem until much later.
- Describe in source documents when you learn of study-relevant information and actions taken when you became aware of information. This demonstrates due diligence.
- Lost to follow-up subjects:
  - Often begins as a missed subject visit or contact. Document missed visits and actions /attempts to follow up.
  - Document final action taken - certified letter, receipt as signed or undeliverable, notice to sponsor and IRB that no further contact will be attempted, record closed.
### Documentation of the Informed Consent Process

<table>
<thead>
<tr>
<th>Study Title:</th>
<th>Date Consent Obtained:</th>
<th>Time:</th>
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<th>Date HIPAA Obtained:</th>
<th>Time:</th>
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**Initial each box below (or indicate not applicable):**

- Discussed, explained and reviewed all elements of the consent form with the participant and/or the participant's Legally-Authorized Representative (LAR).
- Ample time provided for reading the consent document, and the participant (and/or LAR) was encouraged to ask any questions.
- Alternatives to study participation discussed with the participant (and/or LAR).
- All questions and concerns addressed prior to signing of the consent document, and the participant (and/or LAR) is able to demonstrate understanding of what he/she has consented to.

- The participant has agreed to participate in the study, and prior to the start of any study procedures has:
  - Signed/dated a valid consent form (per IRB approved consent process)
  - Given verbal consent (per IRB approved consent process)
  - Legally-Authorized Representative (LAR) has given consent (per IRB approved consent process)
  - Name: _____________ Relationship: _____________

- The consent process was witnessed by a third party (if applicable).
  - Witnessed by: _____________

- A copy of the signed and dated consent and HIPAA Authorization form was given to the participant.

- A copy of the signed and dated consent form was placed in the medical record (if applicable).

- Original signed and dated ICF placed in the participant research file

**Notes:**

- 

- 

- 

**Signature of person obtaining Consent**

**Printed Name of person obtaining Consent**

**Date**

www.mncrp.org
Note to File Template

Note-To-File Template

A note to file should:

- Be generated on a case-by-case basis
- Include the subject and protocol it refers to
- Be signed and dated by the individual who is writing it
- Be legible if handwritten
- Explain clearly and specifically the reason for the error/omission/discrepancy or process/policy it aims to address. Avoid using "one-size-fits-all" notes when providing details. Overuse of a blanket statement will take away from the value of a note to file.
- Be "one-size-fits-all" only when the error/omission/discrepancy is the result of a single, re-occurring oversight/erroneous practice (e.g. failure to provide subject with a signed/dated copy of the consent form) Or when it refers to a general practice such as the filing of regulatory documents in alternate locations/electronically.
- Should include any corrective action or follow-up when applicable.
- Be filed with the document, subject file or behind the study binder tab to which it applies

Sample Note To File:

PROTOCOL #: 2007p098765
TITLE: The Effect of ‘Investigational Product’ on XYZ Levels in Healthy Controls

From: Julie M. Kaberry, research coordinator
To: Subject File
Re: Subject# 015-SAW
Date: October 31, 2007

This subject was consented by Dr. Wolf on October 20, 2007. Dr. Wolf, in error dated the consent form October 19, 2007. The dating discrepancy is not representative of an inappropriate consent process, but the result of a typo. Dr. Wolf has been reminded to confirm the correct date in the future.

Signature:

From Office of Clinical Trials
Template for Progress Notes or PE

PROGRESS NOTES

IRB #

Study Title:

Subject ID#:

___________________________________________________________

___________________________________________________________

___________________________________________________________

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Signature________________________ Date __________
# Telephone Contact Log

**Study ID __________   Subject ID __________**

<table>
<thead>
<tr>
<th>Date/Time</th>
<th>Incoming/Outgoing</th>
<th>Message/Conversation</th>
<th>Comment</th>
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<tbody>
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Maintaining Regulatory Files

• Essential Documents for conduct of Clinical Trial should be maintained together in a **Regulatory Binder**

• Purpose of Regulatory Binder:
  • Organize essential documents
  • Allows research team to reference information
  • Allows easy access to documents by monitor, auditor, IRB, FDA, OHRP

• Principal Investigator ultimately responsible for maintenance of Regulatory Files, but task often delegated to other member of research team
Regulatory Binder (Essential Documents)

- Signature logs (DOA and monitoring log)
- Screening/enrollment logs
  - Protocol and amendments
  - Investigator’s Brochure
- Sponsor correspondence
- Training (GCP, Protocol etc.)
- 1572, Conflict of Interest, CV’s, Licenses, Financial Disclosures
- IRB membership, FWA
- IRB approvals and correspondence
- AE log, SAEs
- IND Safety Reports
- Local Laboratory CLIA/CAP, normal values, Lab Dir. CV
- Temperature Logs
- Subject ID Code List
# Delegation of Responsibility Log

Note: The PI is ultimately responsible for all aspects of the study.

Study IRB#: __________________________
Study Title: ____________________________________________________________________________

Principal Investigator: ____________________________________________________________Coordinator: _______________________

*Record staff responsibilities using the following codes, list all that apply:

- A) Subject Recruitment
- B) Obtains Informed Consent
- C) Performs Study Assessments
- D) Assesses Subject for Adverse Events
- E) Administers Study Medications
- F) Drug, Biologic, or Device Accountability
- G) Data Management
- H) Regulatory Reporting/Paperwork/Maintenance
- I) Packs/ships samples
- J) Other: ___________
- K) Other: ___________________

## Table of Study Personnel Responsibilities

<table>
<thead>
<tr>
<th>Study Personnel Printed Name</th>
<th>Title</th>
<th>Study Personnel Role (e.g. PI, Investigator, Coordinator, Pharmacist, etc.)</th>
<th>Responsibilities* (List all letters that apply)</th>
<th>Signature of Study Personnel</th>
<th>Initials of Study Personnel</th>
<th>Obligation</th>
<th>PI Signature &amp; Date</th>
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## Monitoring Log

**MONITORING LOG**

<table>
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<tr>
<th>Principal Investigator:</th>
<th>Study Title:</th>
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<tbody>
<tr>
<td>UNC Protocol #:</td>
<td>Sponsor:</td>
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<tr>
<th>Date of Monitoring Activity</th>
<th>Description of Monitoring Activity (e.g. meeting **, internal review, external monitoring ***))</th>
<th>PI/Study Staff Signature</th>
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* This log can be used to document any form of activity conducted for the purpose of monitoring study progress
** At minimum record dates and attendance
*** Record name and signature of monitor

From Office of Clinical Trials
## Screening and Enrollment Log

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Telephone Pre-Screen Date</th>
<th>Potentially Eligible ?</th>
<th>Screening Visit Date</th>
<th>Study ID Number</th>
<th>Consented/ Enrolled ?</th>
<th>Eligibility *</th>
<th>Staff Initials</th>
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# Protocol Deviation Log

## Sample Protocol Deviation Log

**Protocol Name:**

---

<table>
<thead>
<tr>
<th>Protocol Deviation Code:</th>
<th>Participant Initials</th>
<th>Participant ID#</th>
<th>Date Deviation Occurred: mm/dd/yyyy</th>
<th>Date Protocol Deviation Form Completed: mm/dd/yyyy</th>
<th>Contact Person (if applicable)</th>
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### SAMPLE PROTOCOL DEVIATION CODES

**Consent Form:**

1. Missing or not obtained
2. Not signed and dated by participant
3. Does not contain all required signatures
4. Outdated, current IRB-approved version not used
5. Not protocol specific
6. Does not include updates or information required by the IRB

**Randomization:**

7. Ineligible participant enrolled and/or randomized
8. Participant is randomized prior to determining whether eligible for study.
9. Occurs outside protocol window

**IRB:**

10. Not reporting a serious complication within 24 hours;
11. Approvals not kept up to date
12. Enrollment and/or treatment occurs prior to IRB approval or during period when on “on hold.”
13. Reportable serious adverse events not reported to IRB
14. Receives wrong treatment
15. Visits occur outside expected follow-up window
16. Entered into another study
17. Missing data and/or forms
18. Missing radiology and/or operative reports
19. Forms or data not sent from clinical site to coordinating center

# Adverse Event Tracking Log

Principal Investigator:  
HRC Protocol #:  
Study Title:  

<table>
<thead>
<tr>
<th>#</th>
<th>Subject ID</th>
<th>Date of Event</th>
<th>Date PI Aware</th>
<th>Description of Event</th>
<th>Serious</th>
<th>Non-serious</th>
<th>Expected</th>
<th>Unexpected</th>
<th>Severity Scale (CTCAE)</th>
<th>Relatedness</th>
<th>Date Reported to IRB, if applicable</th>
<th>Date of IRB Review</th>
<th>Other</th>
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Templates Available for Documentation (NRP or NC TraCS)

- Delegation of Authority (Responsibility) Log
- Protocol Modification Tracking
- Adverse Event (UP) Tracking
- Protocol Violation Log
- Memo to File
- Progress Note Template
- Screening and Enrollment Log
- Telephone Log
- Investigational Drug or Device Accountability
- Consent Process Documentation
Questions?
And for a fun video on compliance, go to

- [https://www.youtube.com/watch?v=wKsdMenonLw&feature=youtu.be](https://www.youtube.com/watch?v=wKsdMenonLw&feature=youtu.be)
INFORMED CONSENT

Marie Rape, RN, BSN, CCRC
Associate Director, Regulatory Service
NC TraCS Institute
Objectives

• Regulatory requirements for Informed Consent
• Review the Informed Consent Document
• Review the Informed Consent Process and documentation of that process
• Discuss difficult situations faced in the consent process
• Review additional required forms for the Informed Consent Process
History

- Nuremberg Code 1947
  - http://www.ushmm.org/research/doctors/codeptx.htm
- Declaration of Helsinki 1964
- Belmont Report 1979
- Code of Federal Regulations (21CFR50 or 45CFR46)
- ICH Good Clinical Practices 1996
Hello, Mr. Sullivan, are you ready for our consent discussion?

Don't tell them you smoke or they won't take you.

Say your family has a history of heart disease.

They pay big $$$, dude!!! lol

FCA inspected and approved
Informed Consent

Both a DOCUMENT and a PROCESS
Informed Consent

ICH Guidelines for Good Clinical Practice (ICH E6) Defines Informed Consent as:

“A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form”
Informed Consent Document

• Consent Form elements / requirements detailed in the Code of Federal Regulations.

• Document - UNC IRB template vs. Sponsor template

• 8 basic elements must be included in all consent forms

• Additional six additional elements that may or may not apply to your study.
8 Basic elements of Informed Consent
Consent 45 CFR 46.116a & 21 CFR 50.25

1. Study involves research, purpose, duration of subject’s participation, procedures, and which procedures are experimental
2. Risk and discomfort
3. Benefits
4. Alternative procedures, available therapies
5. Confidentiality
6. Explanation of more than minimal risk/compensation
7. Contact numbers for questions
8. Voluntary, refusal, may discontinue any time
Additional Elements
(if appropriate)

1. Injury to fetus or breast fed children
2. Circumstances resulting in termination
3. Additional costs to subjects
4. Consequences of withdrawing from the research
5. Significant new findings
6. Number of Subjects
7. Clinicaltrials.gov language when FDA-regulated
Informed Consent Document (Guidelines)

General Requirements: 21 CFR 50:2

• Language understandable to the subject
  ➢ Don’t cut and paste from protocol, too technical
  ➢ Avoid pages and pages of pure text – overwhelming/confusing
  ➢ No medical language
  ➢ Native language (English vs. Spanish)
  ➢ Written at 8th grade level

• Written in second person: “You are being asked to take part in a research study . . .” Investigator is referred to as “I or we”

• No exculpatory language

• Schedule of Events – helpful to include a simplified table
Informed Consent: the Process

- Researcher must obtain legally effective informed consent
- Consent Process involves
  - Providing adequate information regarding study
  - Providing adequate opportunity (time) for subject to consider all options
  - Responding to subject’s questions
  - Ensuring subject’s understanding
  - Ensuring subject’s voluntary agreement to participate
  - Possibility of coercion or undue influence is minimized
  - Providing signed copy to subject, keep original for study files
- Always use most recent version of Consent Form (pull from IRBIS, don’t stockpile copies on desk)
- Consent obtained *before* research begins
Assessing Comprehension

• The fact that a subject signed a consent form does not mean he/she understood what was being agreed to or truly gave their voluntary consent.

• Ask open ended questions:
  • What is the study about?
  • What will you need to do in the study?
  • What are the possible risks in the study?
  • How long will the study last?

• Ask subject to tell you how they would describe to a family member the study and their participation

• Document answers to demonstrate that informed consent was obtained
Observation of the Consent Process

• The UNC IRB is beginning a new program to observe the consent process
• Begins March 2016 with CTRC based studies
• IRB monitor will pre-select potential participants scheduled to be consented:
  • On day of Visit 1, the IRB monitor will ask the PARTICIPANT (not study coordinator) if OK to observe the process and then ask them some questions about the process afterwards.
  • Following completion of the consent process (but before the subject is asked to sign the consent form), the IRB monitor will ask the potential participant a few open-ended questions to assess comprehension.
  • If the potential participant does not successfully answer the questions, the consent process will be deemed invalid and the informed consent process will need to be repeated.
Is it ever acceptable for a member of the IRB to observe the informed consent process at a site?

Yes. The FDA regulations authorize the IRB to observe or have a third party observe the consent process, as well as the research (21 CFR 56.109(f)). According to the informed consent guidance, IRBs should consider using this authority when it believes it is appropriate and will enhance the protection provided to subjects (e.g., when the investigator is also the treating physician for a potential subject, when the person conducting the consent interview is relatively inexperienced, or when the clinical investigation involves vulnerable subjects). In addition to observing a sample of consent interviews, the IRB could interview subjects to assess the consent process and evaluate the subjects’ understanding of the clinical investigation.

Dealing with Difficult Consenting Situations

- Subject who doesn’t really read the form
- Subject who is in a hurry
- Realizing a subject can’t read
- Obtaining assent of children
- Coercion & Undue influence to participate in research
  - **Coercion** occurs when someone feels threatened (inadvertently or intentionally) which leads them to consent to research that otherwise might not be willing to do.
  - **Undue influence** occurs when offer an excessive or inappropriate reward or other means which influences the person to consent (something you can’t turn down).
Minimizing Possibility of Coercion and Undue Influence

- Situations that could unintentionally lead to coercion / undue influence:
  - PI of study is also the patient participant’s MD
    - Patient may readily agree to study due to influence of MD; feel what MD recommends must be best, don’t want to say no to their physician
    - Subject may feel they will lose care of MD or access to health services if does not participate in the research
  - Family of participant present during consent, especially for child who is assenting, or someone of different culture / nationality (male spouse is decision maker).
  - Financial reasons (high payment or lack of insurance & need treatment), especially in those who are poor
  - Class credit for participating in research
Informed Consent: the Process

ONGOING PROCESS

• Re-confirm consent periodically during the study
• Provide updated info as indicated
• A new, IRB approved, informed consent form must be signed every time the risk changes (dictated by IRB, sponsor)
• A revised CF needs to be signed when important info for subject to know - PI changes, contact info changes, protocol activities change (visits, labs, procedures).
• Subjects do NOT need to be re-consented every year, just because. Only re-consent when there are changes that impact their study participation.

• It is not necessary to have a new version date on consent forms each year. The version date should only be updated if the content has been revised.
Documentation of Informed Consent

• Delegation of authority log – who can obtain consent?

• Review signed consent document for completeness
  • Signatures (subject and/or parents/legal guardian, person obtaining consent)
  • Date of consent (written by the person signing, includes subject)

• Document the process in source document and/or medical record:

  “subject was given the consent form and opportunity to read it; the research protocol was reviewed with subject who was given the opportunity to ask questions, and that all questions were answered; the subject was told he could withdraw at any time; we discussed his other options for treatment which were _____; the consent form was signed before any study procedures were performed, and a copy of the signed consent form was given to the subject.”

Suggest including in note the time written consent obtained, especially if study procedures performed same day as consent.

Can also document questions subject asked and answers provided during the consent process.
Dating of Consent Forms

- 21 CFR 50.27 (a) states: “Except as provided in 56.109(c), informed consent shall be documented by the use of a written consent form approved by the IRB and **signed and dated by the subject** or the subject's legally authorized representative **at the time of consent**. A copy shall be given to the person signing the form.”

- ICH GCP E6 4.8.8 also states: “Prior to a subject’s participation in the trial, the written informed consent form should be **signed and personally dated by the subject** or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion.”

- Based on the regulations cited above, the subject **MUST** sign and date the consent document themselves, unless a waiver of written documentation has been granted by the IRB or the use of a legally authorized representative has been approved by the IRB.
Documentation Mistakes with ICF

DO NOT:

• Cross or strike through text or sections in the approved consent form
  • If content no longer relevant to subjects, modify consent form to remove text
• Mark on or write in margins of the consent form
  • i.e., star or circle a section, underline text, write something on a page
  • If need to stress or add content, submit changes to IRB as modification
• Leave the lines for initials or check boxes blank
  • If required that subject initial or check a box to agrees to a procedure (i.e., audio recording), this must be done to make it legally effective consent
  • If consent includes lines for subject to initial each page read, make sure done
• Add additional signature lines to consent form (i.e., for a witness or LAR)
  • If have reason to add a signature line for others to sign, submit modification to the IRB requesting change (IRB needs to approve new consent process)
• Do not use White Out on CF to correct errors!!

If there are special circumstances surrounding the consent process, write a note in subjects chart (not on the form)
Additional Forms for Informed Consent Process

- Storage of samples – for future use (not main study)
- SSN Form – signed by subject giving permission to collect SSN for payment (over $200 per calendar year)
- Assent (pediatrics) & parental permission
- Translated consent documents & interpreters
- Short form – used for blind, illiterate, non-English speaking subjects to document consent and witness
- HIPAA authorization
Health Insurance Portability and Accountability Act – “HIPAA”

• HIPAA is a federal law aimed at protecting health information by establishing standards for the use and disclosure of individually identifiable health information (known as Protected Health Information or PHI) created, received or disclosed by a health care entity.

  • PHI is any information about health status, provision of health care, or payment for health care that can be linked to an individual. This is interpreted rather broadly and includes any part of a patient’s medical record or payment history.

  • When a covered entity discloses any PHI, it must make a reasonable effort to disclose only the minimum necessary information required to achieve its purpose.
HIPAA and Research

- HIPAA requires either a patient authorization or a waiver of the authorization requirement to use identifiable health information (PHI) for research.
- **IRB makes determination if HIPAA privacy laws apply.**
- Most research requires a signed HIPAA Authorization form if accessing a subject’s PHI from medical record.
- **IRB may waive authorization requirement** (signed form) for
  - retrospective chart reviews
  - reviews preparatory to research
  - "de-identified" data sets
  - a limited waiver of HIPAA authorization may be granted by IRB to identify potential subjects for recruitment
Request for Access to Protected Health Information for Research Purposes

- Under HIPAA, UNC Health Care required to document disclosure of protected health information, including for research purposes.
- Researcher required to submit Research Disclosure form if accesses records of fewer than 50 patients:
  - [http://research.unc.edu/files/2014/02/HIM-Research-Disclosure-Form-2014.11.05.pdf](http://research.unc.edu/files/2014/02/HIM-Research-Disclosure-Form-2014.11.05.pdf)
  - Send form to UNC Health Information Management (HIM) with IRB approval letter: fax to 919 595 5590; or call 919-595-5591
  - Send updated form to HIM at each annual renewal
  - The IRB application refers to requirement in C.1 Data Sources and provides link.

- HIM automatically receives data regarding which studies are using medical records and list of staff on those studies. Studies without a full or limited waiver of HIPAA **must** submit to UNC Health Information Management (HIM) the individual consent forms for patients whose records are accessed.
HIPAA - Research Training

- Topic of HIPAA included in the CITI Human Subject Protection (Ethics) training
- UNC SOM requires additional HIPAA training
- **All SOM employees involved in human subject research are** required to take HIPAA Training:
  - **General Privacy and Information Security**
  - Training conducted *initially* upon hire and *renewed annually*
- University **requires** online HIPAA training for new employees and requires annual renewal training, [http://www.unc.edu/hipaa/training.htm](http://www.unc.edu/hipaa/training.htm)
Templates and Forms

For sample templates and forms, see the UNC Office of Clinical Trials Website

• http://research.unc.edu/offices/clinical-trials/resources/forms/

Modify them to fit the specifics of your trial / study
Recommended Reading:

The Immortal Life of Henrietta Lacks

Doctors took her cells without asking. Those cells never died. They launched a medical revolution and a multimillion-dollar industry. More than twenty years later, her children found out. Their lives would never be the same.

Rebecca Skloot