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, Billing Coverage Analysis, Essential Documents

- **Module 4:**
  Recruitment, Budgets and Accounting, Preparing NIH & Industry Grant Budgets, and IDS / Device Policy

- **Module 5:**
  COI, From CDA to Study Close Out

STUDY TEAM RESPONSIBILITIES

Laura Tuttle, MA, CCRP
Assistant Director, Hypertension Research Program
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)
Form FDA 1572 continued

“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
- Project Manager
- Research Associate
- Research Nurse
- 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

Protocol Implementation

"Strength and speed are useful, son, but coordination is crucial!"
Protocol Implementation

Before your study starts, some things to consider:

- Study startup 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.
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

Topics Covered in ICH GCP

Describes:

- 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.

- 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?**

![Image of a document with attributes marked: 9 am, 80, 70, 16, 36°C, Subject 105-0001 ABC 3/1/06]

**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

<table>
<thead>
<tr>
<th>SUBJECT ID:</th>
<th>SCREENING VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Visit:</td>
<td></td>
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<tr>
<td>Date of Eligibility Determined:</td>
<td></td>
</tr>
</tbody>
</table>

SECTION A: INCLUSION CRITERIA

- Patient is between 18 and 55 years old.
- No current history of chronic inflammatory bowel disease, including ulcerative colitis and Crohn’s disease.
- Patient does not have a history of colon polyp removal by colonoscopy.
- Patient has not been treated with chemotherapy or radiation therapy for any reason.
- Patient has no history of polyps or colorectal cancer.
- Patient is not pregnant or nursing.
- Patient or primary caregiver denies a history of prior abdominal surgery.
- Patient has no history of colonoscopy within the last 5 years.
- Patient has normal blood pressure.
- Patient has no history of significant bleeding disorder.
- Patient has no history of prior abdominal surgery.
Signature by PI that Subject is Eligible

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
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.
- 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

IRS #
Study Title:
Subject ID:

From

To

Date

Signature__ Date _____
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 Title:**

**Principal Investigator:**

**Coordinator:**

#### Study Personnel

<table>
<thead>
<tr>
<th>Study Personnel (e.g., Investigator, Coordinator, Pharmacist, etc.)</th>
<th>Responsibilities*</th>
<th>Signature &amp; Date</th>
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<tbody>
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<td></td>
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<tr>
<td></td>
<td>C) Performs Study Assessments</td>
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<td></td>
<td>D) Assesses Subject for Adverse Events</td>
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<td>E) Administers Study Medications</td>
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<td>F) Drug, Biologic, or Device Accountability</td>
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<td></td>
<td>G) Data Management</td>
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<td></td>
<td>H) Other:</td>
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</table>

#### Obligation

PI Signature & Date (To acknowledge roles & responsibilities)

IRB Approved

Start Date

End Date

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### Monitoring Log

**MONITORING LOG**

**Principal Investigator:**

**Study Title:**

**UNC Protocol #:**

**Sponsor:**

#### Description of Monitoring Activity

<table>
<thead>
<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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</thead>
<tbody>
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</tbody>
</table>

*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**

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### Screening and Enrollment Log

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Telephone</th>
<th>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>Screen Failure, Reason</th>
<th>Date</th>
<th>Eligible</th>
<th>Screen Failure, Reason</th>
<th>Date</th>
<th>Eligible</th>
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**From Office of Clinical Trials**
Protocol Deviation Log

Sample Protocol Deviation Log

Protocol Name: __________________________________________________________________________

Protocol Deviation Code: __________________________________________________________________________

Participant Initials: __________________________________________________________________________

Participant ID#: __________________________________________________________________________

Date Deviation Occurred: mm/dd/yyyy

Date Protocol Deviation Form Completed: mm/dd/yyyy

Contact Person (if applicable) __________________________________________________________________________

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

Participant:
14. Receives wrong treatment
15. Visits occur outside expected follow-up window
16. Entered into another study

Study Data and/or Forms:
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

From http://www.nia.nih.gov/ResearchInformation/CTtoolbox

Adverse Event Tracking Log

Principal Investigator: ___________________________ HRC Protocol #: ___________________________
Study Title: __________________________________________

<table>
<thead>
<tr>
<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 (CTCAE)</th>
<th>Relatedness</th>
<th>Date Reported to IRB, if applicable</th>
<th>Date of IRB Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
</tr>
</tbody>
</table>

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?

Documentation / Compliance Video

And for a fun video on compliance, go to
- 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 Informed Consent Process
- Discuss best practices for documentation of consent
- Discuss difficult situations faced in the consent process
- Review additional required forms for consenting subjects
- Review how HIPAA impacts research consent

History

- Nuremberg Code 1947
  - http://www.ushmm.org/research/tobacco/codeptx.htm
- Declaration of Helsinki 1964
- Belmont Report 1979
- Code of Federal Regulations (21CFR50 or 45CFR46)
- ICH Good Clinical Practices 1996
Informed Consent

Both a DOCUMENT and a PROCESS

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 (CFR).

• 8 basic elements must be included in all consent forms

• Seven additional elements that may or may not apply to your study.

• Consent Form Document - UNC IRB template vs. Sponsor template
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 Recommendations:

- Language understandable to the subject (21CFR50.2)
  - 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
  - Schedule of Events – include a simplified table if available

- Written in second person: “You are being asked to take part in a research study . . .” Investigator is referred to as “I or we”
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
  - Consent obtained before research begins
- Always use most recent version of Consent Form

Assessing Comprehension
- Signed Consent does not equal Comprehension!
- Ask open ended questions to evaluate comprehension:
  - 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
March 2016, the UNC IRB began a new program to observe the consent process in CTRC based studies
- IRB monitor pre-selects potential participants scheduled to be consented:
  - IRB monitor asks PARTICIPANT (not study coordinator) if OK to observe the process and ask them some questions about the process afterwards.
  - Following completion of the consent process (but prior to subject signing consent form), IRB monitor asks the participant a few open-ended questions to assess comprehension.
  - If participant does not successfully answer the questions, the consent process will be deemed invalid and the informed consent process will need to be repeated.
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 of participants
  - Coercion occurs when someone feels threatened (inadvertently or intentionally) which leads them to consent to research they 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 may unintentionally lead to coercion / undue influence:
  - PI of study is also the MD of patient participants
    - Patient may readily agree to study due to influence of MD: “what MD recommends must be best” or have trouble saying no to their physician
    - Subject may worry they will lose care of MD or access to health services if don’t participate in the research
  - Family of participant present during consent
    - Parent with assenting child, or someone of different culture / nationality where male spouse is decision maker.
  - Financial reasons in those who lack resources
    - high payment, treatment offered to those who lack insurance
    - Class credit for participating in research

Informed Consent: the Process

- ...ongoing process
  - Re-confirm consent periodically during the study
  - Provide updated info to subjects 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. Only re-consent when there are changes that impact their study participation.
  - Not necessary to have a new version date on consent forms each year - version date only updated if the content has been revised.
Documentation of Informed Consent

- Delegation of authority log – is the consenter listed on the log?

- Review signed consent document for completeness
  - Signatures of subject, parents, legal guardian and person obtaining consent
  - Date of consent (written by person signing)

- Document consent process in source document 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.

  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."

- 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 above regulations, 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 agree 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

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**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.

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**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
  - 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
  - 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.
- Can also access UNC Health Care data, PHI by going through the Carolina Data Warehouse

HIPAA - Research Training

- CITI Human Subject Protection (Ethics) training includes some info on HIPAA
- UNC SOM requires additional HIPAA training: All SOM employees involved in human subject research are required to take the following:
  - General Privacy and Information Security
  - Final HIPAA Omnibus Rule Special Training: http://www.med.unc.edu/security/hipaa/final-omnibus-rule-training
  - 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

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