ORIENTATION FOR NEW CLINICAL RESEARCH PERSONNEL

MODULE 1

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, Documentation and GCP, Informed Consent

• **Module 3:**
  Contracting, Billing Coverage Analysis, ClinicalTrials.gov, Budgets and Accounting, Essential Documents

• **Module 4:**
  COI, Epic requirement for training, Preparing & Executing NIH Grant Budgets, and IDS / Device Policy

• **Module 5:**
  Recruitment, From CDA to Study Close Out
Overall Objectives

- Define human subject / clinical research
- Discuss various options available for training of research personnel
- Review human subject research protection and the IRB
- Define appropriate responsibilities for study team members
- Describe steps for successful implementation of a study
- Describe appropriate management of study documentation
- Define Good Clinical Practices (GCP)
- Review the informed consent process including HIPAA
- Discuss research compliance and required approvals at UNC
- Review basic elements of contract negotiation and grant management
- Describe steps for managing budgets and accounting of funds
- Describe steps for preparing and executing NIH grant budgets
- Describe good recruitment practices and support available at UNC
- Review best practices for preparing and executing NIH grant budgets
- Describe how to implement a clinical trial from CDA to study closure
<table>
<thead>
<tr>
<th>Speaker</th>
<th>Office / Dept. Represented</th>
<th>Phone number</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marie Rape</td>
<td>NC TraCS</td>
<td>919-966-6844</td>
<td><a href="mailto:Marie_rape@med.unc.edu">Marie_rape@med.unc.edu</a></td>
</tr>
<tr>
<td>Laura Tuttle</td>
<td>Family Practice</td>
<td>919-966-2881</td>
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<tr>
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<td>919-966-1594</td>
<td>chcoley#@email.unc.edu</td>
</tr>
<tr>
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<td><a href="mailto:juanita_cuffee@med.unc.edu">juanita_cuffee@med.unc.edu</a></td>
</tr>
<tr>
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<td><a href="mailto:buchholz@unc.edu">buchholz@unc.edu</a></td>
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<tr>
<td>Christine Nelson</td>
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<td>919-843-0832</td>
<td><a href="mailto:chrisnel@email.unc.edu">chrisnel@email.unc.edu</a></td>
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<tr>
<td>Nina Cannon</td>
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<td>919-962-8531</td>
<td><a href="mailto:ninac@email.unc.edu">ninac@email.unc.edu</a></td>
</tr>
<tr>
<td>Monica Coudurier</td>
<td>OCT / CT.gov</td>
<td>919-843-2333</td>
<td><a href="mailto:m_coudurier@unc.edu">m_coudurier@unc.edu</a></td>
</tr>
<tr>
<td>Andrea Eiring</td>
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<td>919-843-2698</td>
<td><a href="mailto:aneiring@email.unc.edu">aneiring@email.unc.edu</a></td>
</tr>
<tr>
<td>Jill Cunnup</td>
<td>Budgeting</td>
<td>919-966-0134</td>
<td><a href="mailto:Jillyan_cunnup@med.unc.edu">Jillyan_cunnup@med.unc.edu</a></td>
</tr>
<tr>
<td>Joy Bryde</td>
<td>COI office</td>
<td>919-843-5328</td>
<td><a href="mailto:jbryde@email.unc.edu">jbryde@email.unc.edu</a></td>
</tr>
<tr>
<td>Carol Breland</td>
<td>Recruitment</td>
<td>919-966-6274</td>
<td><a href="mailto:brelandc@email.unc.edu">brelandc@email.unc.edu</a></td>
</tr>
<tr>
<td>Sue Pope</td>
<td>Invest. Drug</td>
<td>919-966-2371</td>
<td><a href="mailto:Spope@unch.unc.edu">Spope@unch.unc.edu</a></td>
</tr>
<tr>
<td>Sandy Barnhart</td>
<td>Ophthalmology</td>
<td>919 843-0076</td>
<td><a href="mailto:Sandy_barnhart@med.unc.edu">Sandy_barnhart@med.unc.edu</a></td>
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</table>
# Knowing the Resources Available

<table>
<thead>
<tr>
<th>Topic</th>
<th>Unit/Office</th>
<th>Website</th>
<th>Telephone</th>
</tr>
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<tbody>
<tr>
<td>Training for Research Staff</td>
<td>Network for Research Professionals (NRP)</td>
<td><a href="http://nrp.tracs.unc.edu/">http://nrp.tracs.unc.edu/</a></td>
<td>na</td>
</tr>
<tr>
<td>Resources, NRP, CRMS, upcoming events</td>
<td>Research Central</td>
<td><a href="http://researchcentral.tracs.unc.edu/">http://researchcentral.tracs.unc.edu/</a></td>
<td>na</td>
</tr>
<tr>
<td>Online IRB application</td>
<td>OHRE</td>
<td><a href="https://apps.research.unc.edu/irb/">https://apps.research.unc.edu/irb/</a></td>
<td>na</td>
</tr>
<tr>
<td>Human subjects research, GCP, and RCR training</td>
<td>CITI on-line training</td>
<td><a href="http://research.unc.edu/offices/human-research-ethics/researchers/training/index.htm">http://research.unc.edu/offices/human-research-ethics/researchers/training/index.htm</a></td>
<td>na</td>
</tr>
<tr>
<td>HIPAA Policies, Training</td>
<td>HIPAA online Training</td>
<td><a href="http://www.med.unc.edu/security/hipaa">http://www.med.unc.edu/security/hipaa</a></td>
<td>na</td>
</tr>
<tr>
<td>Research facts and figures about UNC</td>
<td>UNC Research</td>
<td><a href="http://research.unc.edu/index.htm">http://research.unc.edu/index.htm</a></td>
<td>na</td>
</tr>
<tr>
<td>Sponsored projects</td>
<td>Office of Sponsored Research (OSR)</td>
<td><a href="http://research.unc.edu/offices/sponsored-research/index.htm">http://research.unc.edu/offices/sponsored-research/index.htm</a></td>
<td>919-966-3411</td>
</tr>
<tr>
<td>Proposal &amp; Award Development</td>
<td>RAMSeS</td>
<td><a href="https://apps.research.unc.edu/ramses/">https://apps.research.unc.edu/ramses/</a></td>
<td>919-966-3411</td>
</tr>
<tr>
<td>Clinical Trials, Contracts, CT.gov</td>
<td>Office of Clinical Trials</td>
<td><a href="http://research.unc.edu/offices/clinical-trials/index.htm">http://research.unc.edu/offices/clinical-trials/index.htm</a></td>
<td>919-843-2698</td>
</tr>
<tr>
<td>Investigational Drugs</td>
<td>Investigational Drug Service (IDS)</td>
<td><a href="http://pharmacy.intranet.unchealthcare.org/services/investdrugs">http://pharmacy.intranet.unchealthcare.org/services/investdrugs</a></td>
<td>843-9919, (manager)</td>
</tr>
<tr>
<td>Clinical research support/Guidance</td>
<td>NC TraCS</td>
<td><a href="http://tracs.unc.edu/">http://tracs.unc.edu/</a></td>
<td>966-6022</td>
</tr>
<tr>
<td>Submission Tool, 98 budgeting</td>
<td>Clinical Research Management System</td>
<td><a href="http://researchcentral.tracs.unc.edu/index.php/use-crms">http://researchcentral.tracs.unc.edu/index.php/use-crms</a></td>
<td>843-0726 (Laura)</td>
</tr>
<tr>
<td>Clinical Research Unit</td>
<td>CTRC</td>
<td><a href="http://tracs.unc.edu/index.php/performresearch/about-ctrcc">http://tracs.unc.edu/index.php/performresearch/about-ctrcc</a></td>
<td>843-1070</td>
</tr>
<tr>
<td>Cancer Research</td>
<td>Lineberger Comprehensive Cancer Center (LCCC)</td>
<td><a href="http://unclineberger.org/">http://unclineberger.org/</a></td>
<td>919-966-3036</td>
</tr>
</tbody>
</table>
Who should attend Orientation?

- Personnel involved in clinical research
  - Study coordinator
  - Social/Clinical research assistant
  - Research nurse
  - Research associate
  - Regulatory personnel
  - Investigators

- Involved in any type of clinical research
  - Clinical trials
  - Investigator initiated research
  - Federal grants
  - Social / behavioral research
Training, Training, Training

Study personnel are key to conducting quality research!

- Knowledge of research best practices, good clinical practices, keeping abreast of regulatory requirements, and training needs are key to conducting quality research.
- You need to take responsibility for staying informed and educated!

Recommended Trainings

- CITI Good Clinical Practice (GCP) Training, [www.citiprogram.org](http://www.citiprogram.org)
  - required if working with clinical trials

- CITI Ethics Online Course (IRB modules), [www.citiprogram.org](http://www.citiprogram.org)
  - required if involved in human subject research
STUDY COORDINATOR
EDUCATION

Juanita Cuffee, MPH
Pediatrics – Hematology/Oncology
Chair, NRP
Why Coordinator Education?

Responsibility of the investigator to ensure that any individual to whom a task is delegated is qualified by education, training and experience (and state licensure where relevant) to perform the delegated task.

Documentation of training is essential for meeting the guidelines put forth by regulatory agencies for the conduct of Human Subject Research.
Study Coordinator Education

Documentation of coordinator education may be part of the investigator/department/division/center processes. This may include (dependent on type of research being conducted):

• Completion of Human Research Ethics Training
• Completion of Good Clinical Practices Training
• CV and/or state licensure
• Job Skill Training (such as conducting an EKG)
• Training plan per your specific job title
• Documentation of Training for each protocol (training logs)
## Example: Training & Education Checklist

### DCC Staff Competency Check Off

<table>
<thead>
<tr>
<th>Skill</th>
<th>Observation (initial/date)</th>
<th>Competency (initial/date)</th>
<th>NOTE (study/subject)</th>
<th>Site Director (initial/date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Review sponsor sample informed consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Compare AEs and SAEs in IB to risk section in sponsor’s ICF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Review ‘research related injury’ language</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Confirm that patient payments match study budget</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Identify required signatures (subject/LAR/assent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Presenting Informed Consent Form to Subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Give subject Informed Consent Form to take home or read in the office in a private space</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Give subject a highlighter and ask them to highlight any questions they may have throughout the form</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Give the subject ample time to read the form</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Reviewing the Informed Consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Explain each section of the Informed Consent to the subject paying particular attention to the Risks/Benefits/Study Procedures sections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Give subject opportunity to ask any questions of the CRC and/or PI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Obtain appropriate signature(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Subject (Consent or Assent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Legally Authorized Representative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Caregiver</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>d. Once all questions are answered, and subject agrees to participate, ask subject to initial, sign, and date the Inform Consent Form accordingly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Complete any other required signatures for that form (PI, CRC, etc.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>f. Review the form to check for accuracy and correct any errors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>g. Make a copy of the form to give to the subject to take home</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Documenting the Informed Consent Process</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Write a detailed clinical note documenting that each part of items 2 and 3 (above) were done</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Include patient specific information such as who was present during the Informed Consent process, questions asked, answers given, etc.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Always document that the PI was either present or available during the Informed Consent process</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Complete Informed Consent Form and attach to signed ICF in research record</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Obtain informed consent from vulnerable subject populations</td>
<td></td>
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</tr>
</tbody>
</table>

### C. Scheduling/Screening

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Original: October 11, 2010
**Example Matrix of Training**

### UNC Diabetes Care Center

#### Delegation of Responsibilities Table

<table>
<thead>
<tr>
<th>Clinical Trial Activity</th>
<th>MD</th>
<th>PA</th>
<th>NP</th>
<th>RN/LPN</th>
<th>Coordinator per completion of training</th>
<th>Non-medically qualified personnel</th>
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</thead>
<tbody>
<tr>
<td>Pre-Screening Activities</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Informed Consent</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NO</td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
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<td>Medical Evaluations</td>
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<td>X</td>
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<td>NO</td>
<td>X</td>
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<td>Venipunctures</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>ONLY IF CERTIFIED</td>
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<td>Processes and Shipping Laboratory Samples</td>
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<td>Laboratory value assessments</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>IV, SC, IM, PO administration of Investigational Product</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NO</td>
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<tr>
<td>Adverse Event/SAE Causality</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NO</td>
</tr>
<tr>
<td>AE/SAE Assessment to Relationship to Drug</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NO</td>
</tr>
<tr>
<td>SAE Determination per protocol guidelines</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NO</td>
</tr>
<tr>
<td>SAE/AE Reporting to Sponsor and IRB</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>NO</td>
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<tr>
<td>Height, Weight, Hip Measurement, Waist Measurements</td>
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<td>X</td>
<td>X</td>
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<td>Vitals</td>
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<td>X</td>
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<td>NO</td>
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</tbody>
</table>
Study Coordinator Education

OHRP – Office of Human Research Protection

Responsibilities of UNC

• Before any human subjects research can be conducted, the institution must provide the department or agency a **written Assurance** that it will comply with the requirements of the Policy [www.hhs.gov/orhp](http://www.hhs.gov/orhp/)

• The HHS regulations are intended to implement the basic ethical principals governing the conduct of human subject research

General Responsibilities

All parties involved, institution, investigator, and IRB must actively engage in ensuring human subject protection and this is only achieved through **proper training/education** of all research professionals
The purpose of the UNC-NRP is to promote excellence in the conduct of clinical, social, behavioral, and translational research through education, professional development and mentoring.
NRP Educational Programs

- Monthly educational seminars
- Phlebotomy training
- Peer-to-Peer support for new coordinators
- Certification study groups - ACRP & SoCRA
- Listserv for all individuals involved in human subjects research (unc.crc listserv)
  - Informational emails directed specifically to research professionals
  - “Did You Know” emails
  - Educational opportunities
  - Contact Juanita Cuffee to join
Current Projects

- Updating NRP website
- Hands on education seminars
- Organizing communications committee
- Including more social/behavioral research topics
- Planning 2017 monthly educational seminars

NRP is here for you!
Please let us know what you need to do your job better!
Upcoming Training:

NRP Educational Training Session:

EPIC Tips: A Hands on Seminar

Date: October
Time: TBD

Location: Brinkhous-Bullitt, room 219
Who to Contact

• To join the list serv, contact Juanita Cuffee at Juanita_cuffee@med.unc.edu

• To serve on a committee, contact the committee chair

• Information regarding committees and upcoming events can be found on our web site

www.uncnrp.org
INTRODUCTION TO THE IRB

Charlotte Coley, MACT, CIP, Education & Training Manager
Office of Human Research Ethics
Institutional Review Board
Discussion Points

- What is a HRPP?
- History & Why Regulations Were Written
- Ethical Guidelines
- Federal Regulations & Guidelines
- IRB Function

- Understanding Waivers
- Ups & Other Reportable Events
- Reliance Agreements
- Navigating the IRB Application & Submission Process
- Navigating the IRB Website
Objectives

- Learn about history, structure and function of IRB
- Become familiar with:
  - The IRB Website
  - IRB applications
  - Investigator responsibilities following IRB approval
  - Research-related institutional responsibilities
  - Application “hot-spots”
  - Creating consent documents
  - Waivers
  - Reliance agreements
Why are there Federal Regulations?

Why are there IRBs?

Where do they fit in the larger scheme?

What is an HRPP?
WHAT IS A HRPP*?

*Human Research Protection Program
UNC was first awarded accreditation in 2009.
Re-accreditation due in 2017
Office of Human Research Ethics (OHRE)

Responsible for ethical and regulatory oversight of research at UNC-CH that involves human subjects.

The OHRE administers, supports, and guides the work of the Institutional Review Boards (IRBs) and all related activities.

Association for the Accreditation of Human Research Protection Programs, Inc.

AAHRPP accredited since 2009
Research Design Challenge

Then--1974

Now----

45CFR4
6
21CFR
50 & 56
Plus -- 21st Century Challenges

1. Science
2. Technology
3. Ethics

4. NRPR \hspace{1cm} \text{FINAL RULE?}
The Challenge

“Sometimes, with the best of intentions, scientists and public officials... working for the benefit of us all, forget that people are people. They concentrate so totally on plans and programs, experiments, statistics- on abstractions- that people become objects, symbols on paper, figures in a mathematical formula...”

Atlanta Constitution, July 27, 1972
The Challenge: Can you see the forest or the trees?
What Color is Your Lab Coat?
IRB is Often Seen as a Black Hole: a Mystery & a Nuisance

Come visit an IRB Meeting to better understand the process.
HISTORY & WHY THE REGULATIONS WERE WRITTEN
Example of Bad Behavior that led to the Regulations

- Regulations created after a problem
- Rare that laws, regulations, created

Result
It wasn’t just Nazi doctor,
And it didn’t stop
50 years ago….

Time cover of April 22, 2002
Deaths of Research Subjects

- Johns Hopkins University
- University of Rochester
- Lidocaine overdose
- Healthy Subject on an Asthma Study (Ellen Roche)

- University of Pennsylvania
- Institute for Human Gene Therapy

- Jesse Glesinger and 18-year-old with mild OTC deficiency
FDA Audit Findings @ Hopkins

• "… an investigation into the death of a healthy volunteer…"

• "You failed to submit an IND…"

• "You did not supply adequate animal toxicity data"

• "You failed to submit a summary of previous human studies"

• "…you failed to promptly report unanticipated problems…"
End of 20th & Beginning of 21st Century Deficiencies have led to suspensions of research by federal regulatory agencies

- University of Minnesota
- UCLA
- University of Rochester
- Rush Presbyterian
- West LA, VA Hospital
- Duke University
- University of Ill - Chicago
- U Colorado Hlth Sci
- VCU/MCV
- University of S Florida
- UA-Birmingham
- University of Pennsylvania
- University of Oklahoma
- UTMB-Galveston
- Johns Hopkins

Who’s Next? UNC????
OHRP Determination Letters

OHRP has implemented a practice to redact from compliance oversight determination letters posted on its website any sections that discuss unresolved concerns, questions, or allegations related to an ongoing investigation. Anyone wishing to request an unredacted copy of these letters should submit a request for the unredacted letter under the Freedom of Information Act (FOIA). Individual requests will be considered on a case-by-case basis. Such requests should be directed to:

**Public Health Service FOIA Office**
5600 Fishers Lane, Rm 19-01
Rockville, MD 20857
Main telephone number: (301) 443-3403
Main fax number: (301) 460-5662
Email: FOIARequest@psc.hhs.gov

Click on the year of interest below to see a list of the determination letters issued during that year. From that list you can access the redacted content of individual letters.
Headlines found on the Internet Over a Several Years’ Span About Robert Gallo, MD

- Federal Inquiry Finds Misconduct by a Discoverer of the AIDS Virus
- In Gallo Case, Truth Termed a Casualty
- Nobel board bypasses U. Md.’s Gallo
- America hoists the white flag in the HIV war
- The strains of the HIV war
- Was Robert Gallo robbed of the Nobel Prize?
- AIDS Viral Discovery Again at Issue
ETHICAL GUIDELINES

Nuremburg Code
Helsinki Code
Belmont Report
The Belmont Report

- **Respect for persons**: Voluntary Informed consent
  - Individual autonomy
  - Protection of vulnerable people & individuals with reduced autonomy
  - Protection of privacy

- **Beneficence**: Assessment of risks & benefits
  - Maximize benefits & minimize harms
  - Valid study design
  - Competent investigators

- **Justice**: Selection of subjects
  - Equitable distribution of research costs & benefits
  - Unbiased subject selection
  - Fair recruitment
FEDERAL REGULATIONS & GUIDELINES

Health & Human Services (HHS)
- Common Rule
- Food & Drug Administration (FDA)
- Health Information Portability & Accountability Act (HIPAA)
- International Code of Harmonization (ICH)
- Good Clinical Practice (GCP)
Where do the regulations come from?
The Government of the United States

**The Constitution**

**Legislative Branch**
- The Congress
  - Senate
  - House
- Architect of the Capital
- US Botanical Garden
- General Accounting Office
- Library of Congress
- Congressional Budget Office

**Executive Branch**
- The President
- The Vice President
- Executive Office of the President
- Council of Economic Advisors
- National Security Council
- Office of Management and Budget
- Office of Policy Development
- Office of Science and Technology

**Judicial Branch**
- US Supreme Court
- US Court of Appeals
- US District Courts
- US Tax Court
- US Court of Appeals for Veterans Claims
- Administrative Offices of the US Courts

**Departments**
- Department of Education
- Department of Commerce
- Department of Defense
- Department of Education
- Department of Energy
- Dept Health and Human Services
- Dept Homeland Security
- Department of the Interior
- Department of Justice
- Department of Labor
- Department of State
- Department of Transportation
- Department of the Treasury
- Dept of Veterans Affairs
This is not a complete org chart!

The Secretary

Office of Public Health and Science (OPHS)

Office of Human Research Protections (OHRP)
• 45 CFR 46
• "Common Rule"

Office of Research Integrity (ORI)
• Research misconduct issues
• FOIA

National Institutes of Health (NIH)

Centers for Disease Control and Prevention (CDC)

Food and Drug Administration (FDA)
• 21 CFR 50
• 21 CFR 56

Office of Civil Rights
• HIPAA Oversight
  • 21 CFR 160
  • 21 CFR 164

Inspector General

Slide courtesy of Susie Hoffman, UVa
Current Regulatory Structure Creates a “Patchwork Quilt” of Protections

- Not federally funded
- Not FDA regulated
- Not at institution that voluntarily applies 45 CFR 46 to all research via FWA

DHHS
45 CFR 46
Subpart A ➔ Common Rule
Subpart B
Subpart C
Subpart D

Federally Funded
17 Departments & Agencies
Federal Regulations

- Department of Health and Human Services (DHHS)
  - 45 CFR 46
    - **Subpart A** (Basic Policy for Protection of Human Research Subjects) – COMMON RULE
    - **Subpart B** – Pregnant women, fetuses, neonates
    - **Subpart C** – Prisoners
    - **Subpart D** – Children
  - Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule

- Food and Drug Administration (FDA)
  - 21 CFR 50 - Informed Consent
  - 21 CFR 56 - IRBs
  - 21 CFR 312 - Investigational New Drug (IND) Application
  - 21 CFR 812 - Investigational Device Exemptions (IDE)
  - International Conference on Harmonization (ICH) Good Clinical Practice (GCP)
FDA (Food and Drug Administration) Regulations Related to Human Research

Are also subject to FDA regs if data will be submitted as an application to FDA for approval of a new drug, device or biologic:

- Drugs (including nutritional supplements)
- Devices (including mobile apps, software, etc)
- Biologics
HHS.gov: Office for Human Research Protections

http://www.hhs.gov/ohrp/compliance-and-reporting/index.html#
IRB FUNCTION
What is an IRB? (Institutional Review Board)

• A committee mandated by federal regulations.

• Protects the rights and welfare of human subjects in research activities through independent review of proposed research.

• Independent committee formally designated to review, approve and monitor research involving humans.
What is an IRB?

- Institutional Review Board – *Institutional IRB*
- Independent Review Board – *Commercial IRB*
  - *AKA* Independent Ethics Committee (IEC)
  - *AKA* Ethics Review Committee (ERC)
IRB Mission Statement

The University of North Carolina at Chapel Hill is committed to expanding and disseminating knowledge for the benefit of the people of North Carolina and the world. An important part of that commitment to knowledge is research of the highest quality on all aspects of the health and behavior of people, and such research is only possible through the participation of humans as research subjects. Human subjects are partners and participants in research and a precious resource to the university. At UNC-Chapel Hill, human subjects research is a privilege, but not a right.
IRB Membership

• > 5 members
• Most UNC IRBs have 10-15 members
• Not all members of one profession
• No all male or all female
• At least one scientist, one non-scientist
• At least unaffiliated member
• Expertise appropriate
UNC IRB Committees

- **Biomedical (A,B,C,D):** Biomedical research (clinical trials, pharmacological research, etc.) B and D only—Dental and Oncology

- **Non-Biomedical (E):** Behavioral and social sciences; including public health and nursing

- **“Special Issues”:** Compliance issues
The IRB as “Gate keeper”

Serves as the “gate keeper”/monitor to ensure compliance with Institutional Responsibilities:

- Radiation Safety
- Investigational Drug Services
- Institutional Bio-safety
- Ethics training
- Conflict of Interest
- Privacy Office
- Office of University Counsel (OUC)
IRB Office Basic Facts

- ~ 6000 active protocols/year
- ~12,000 activity items/year
- 6 IRBs
- 6 IRB Chair and Vice-Chairs
- 2 Senior IRB Analysts & 6 IRB Analysts
- 4 Managers: QA/QI; Compliance; Education & Training and Data & Information
- 4 Administrative staff
Routing of IRB Submissions

*Note that student research will follow the same routing process as any project.*
Others may review protocols before the IRB, depending on area and focus of research

➤ DEPT- OR SCHOOL-BASED REVIEWS
  • Exercise & Sport Science
  • Psychology
  • Geography
  • Urban & Regional Studies
  • Anthropology
  • Sociology
  • Computer Science
  • City & Regional Planning
  • Ctr for Developmental Science
  • Frank Porter Graham Child Dev.
  • Kenan-Flagler Business School
  • Sch of Information & Library Science
  • Sch of Journalism & Mass Comm
  • Sch of Social Work
  • Sch of Government
  • Sch of Education
  • Office of the President

➤ NIH-MANDATED CENTER REVIEWS
  • Lineberger Comp Cancer Ctr (PRC)

➤ UNIVERSITY OFFICES OR OFFICIALS
  • Office of University Counsel
  • Research Compliance Officer
  • Office of Sponsored Research
  • Office of Clinical Trials

➤ CONFLICT OF INTEREST COMMITTEES
  • SOM
  • Arts & Sciences
  • Institutional COI

➤ OTHER COMMITTEES OR GROUPS

Institutional Biosafety
Radiation Safety
Investigational Drug Service
Data and Safety Monitoring Board (SOM)
HIPAA Privacy Officers, PHI Custodians

➤ EXTERNAL TO UNC

NC Dept. of Correction
EPA
New Scientific Review Process at UNC

- **September 2, 2016**: All clinical research conducted at the University of North Carolina at Chapel Hill involving greater than minimal risk must be submitted for review to the UNC Scientific Review Committee.

- **Beginning Monday, September 19, 2016** any new study submitted for IRB review will be required to have scientific review completed and documented prior to the review.

- [New Scientific Review Process at UNC - UNC Research](#)
Scientific Review

• Not the sole responsibility of the IRB

• Bad science = Bad ethics

• If not scientifically valid, how does one justify the risks?

• Regulations require IRBs to evaluate Risk: Benefit; requires understanding of the science

• Clinical Equipoise – A state of genuine uncertainty regarding the comparative therapeutic merits of each arm in a trial. The requirement of \textit{clinical equipoise} is satisfied if there is genuine uncertainty about the preferred treatment.

OHRE SOP 24.11
Definitions

• **Research:** a *systematic* investigation designed to develop or contribute to *generalizable* knowledge

• **Human subject:** a *(living)* individual about whom an investigator conducting research obtains:
  • Data through intervention or interaction with the individual,
  
  OR

  • Identifiable private information

* HIPAA (Health Insurance Portability & Accountability Act of 1996) Change
Intervention & Interaction

**Intervention:**

1) Physical procedures by which data are gathered (e.g., venipuncture)

2) Manipulations of subject or subject environment for research (e.g., noise while completing a task vs. no noise while completing a task)

**Interaction:** Communication or interpersonal contact between researchers and subject
Existing Data

OHRP's interprets "existing data, documents, records, pathological specimens, or diagnostic specimens" as data, documents, records, pathological specimens, or diagnostic specimens that exist at the time the research is proposed.
Identifiable Data

From 45 CFR 46.102(f):

• …information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects

• Regulations don’t define “readily ascertainable” however, 2004 OHRP Guidance on Coded Information or Specimens defines “readily ascertainable”…
“Readily Ascertainable”

Investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example:

(a) the **key to decipher the code is destroyed before the research begins**;

(b) the investigators and the holder of the key enter into an **agreement prohibiting the release of the key** to the investigators under any circumstances, until the individuals are deceased;

(c) there are **IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key** to the investigators under any circumstances, until the individuals are deceased; or

(d) there are **other legal requirements** prohibiting the release of the key to the investigators, until the individuals are deceased.
Levels of IRB Review

Note: The level of review is determined by IRB, not by the investigator or by the client. The requirements for each level are given in the regulations.

1. Is it Research?
2. Does research include Human Subjects?
3. Is it on the list of exempt categories?
4. Is it on the list of expedited categories?

RISK

Not Human Subjects Research

“Exempt” from continuing review

Expedited Review

Full board review
ii any disclosure of the human subjects’ responses outside the research could *reasonably* place the subjects at risk of

- criminal or
- civil liability or
- be damaging to the subjects’ financial standing, employability, or reputation.”
Is it research?

- **Yes**: Are human subjects involved?
  - **Yes**: Is it exempt from continuing review?
    - **Yes**: Research may be exempt from continuing review
    - **No**: Does it meet criteria for expedited review?
      - **Yes**: Review may be expedited
      - **No**: Requires Full Board Review
  - **No**: NHSR--**IRB review not required
- **No**: Not research--IRB review not required

If you are unsure, submit to the IRB.
NHSR Determination

➢ Does not meet definition of human subjects research

Not Human Subjects Research (NHSR) includes things like…

✔ Interview for campus newspaper
✔ Review of billing data without collection of identifiers
✔ Research of leftover cadaver specimens
✔ Case studies
✔ Quality Improvement projects

**Important:** Although IRB review is not required to make a NHSR determination, if you are unsure you should complete and submit an application to the IRB. An incorrect assessment could result in inability to publish results (or worse).
Exempt Research

- Involves no greater than minimal risk*
- Must be “on the list” (45 CFR 46.101(b)(1)-(6))
- Determination by IRB Chair or designee
- IRB may choose to provide additional measures of protection
- The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review (expedited or convened) utilized by the IRB

*Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. 21 CFR 56.102 (i)
Exempt Research*

1. Normal educational practices in established educational settings
2. Educational tests, surveys, interviews, or observation of public behavior - unless identified & sensitive**
3. Research on elected or appointed public officials or candidates for public office
4. Research using existing data, if publicly available or recorded without identifiers
5. Evaluation of public benefit service programs
6. Taste and food quality evaluation and consumer acceptance studies

* Exception for prisoners
** Exception for children
Expedited IRB Review

- Involves no greater than minimal risk or...
- Involves a minor change in previously approved research
- May be carried out by IRB Chair or designee
- IRB may choose to provide additional measures of protection
- Described in (45 CFR 46.110 and 21 CFR 56.110)—must be “on the list” (63 FR 60364-60367, November 9, 1998)
- Additional pre-review may be required; dependent on department/center
Research requiring full board review

- Involves issues that do not qualify for exempt or expedited review

- Additional pre-review may be required; dependent on department/center
  - Protocol Review Committee (PRC)—Studies involving oncology patients
  - Scientific Review Committee (SRC)—Investigator-initiated research
Criteria for IRB Approval

1. Risks minimized
2. Favorable risk : benefit ratio
3. Equitable selection of subjects
4. Informed consent sought
5. Informed consent documented
6. Monitoring plan for safety
7. Privacy and confidentiality protected
8. Additional safeguards for vulnerable populations

45 CFR 46.111 & 21 CFR 56.111
OHRE SOP 24.0
The IRB Meeting -- Possible actions

- Approved
- Minor contingencies required for approval
- Deferred (major changes required)
- Disapproved
When You Get a Contingency Memo…

• Don’t despair

• Don’t take it personally

• It is rare for an initial proposal not to raise at least one question from the IRB

• The PI should respond to each contingency by responding to the stipulation AND making the corresponding changes to the application and/or consent forms.

• If you believe that the IRB misinterpreted or did not fully understand the information you provided, or you don’t understand a stipulations; you should call the office. Ask to speak with the IRB Analyst at whose meeting your study was reviewed.
When You Get a Contingency Memo:

1. Please make any requested changes to the application, consent forms or attachments ... or explain why changes were not made ...AND...
2. Provide a response to each stipulation explaining how it was addressed, even if only stating "changes made," before resubmitting your revised submission. This will constitute your point-by-point response.
3. When all changes and responses are complete, please click the RESUBMIT button at the lower left.
Approved!

• Research may proceed upon receipt of written documentation of IRB approval

• Investigator has a responsibility to report to the IRB:
  • Changes **BEFORE** they are implemented
  • Protocol violations
  • Protocol deviations (summarize at continuing review)
  • Any unexpected problems involving risks to subjects or others (including unresolved subject complaints)
Protocol modifications

- All protocol changes must be approved by the IRB before implementation.

- All changes to documents used with subjects (consent forms, questionnaires, recruitment materials, etc.) must be approved by the IRB before use.

- The IRB assesses if the modification changes the level of risk:
  
  - Do subjects need to be made aware of the new information? Which subjects?
  
  - If a revised consent form necessary, has it been included; is it accurate?
Continuing Review or “Renewal”

- No approval is valid for longer than one year from the initial review—depending on risk level, could be a shorter review period.

- Expired (lapsed) approval = no approval

- Must meet same criteria for approval as at initial review
Continuing Review or “Renewal”

The IRB assesses whether the study is proceeding as expected:

- Is the number of subjects enrolled \(<\) the number previously approved by the IRB?
- Is there new information that suggests a change in Risk : Benefit?
- Are there trends in protocol deviations that may need to be addressed?
- Do monitoring or DSMB reports suggest issues that may need to be addressed?
- Are there changes requested for the upcoming approval period?
- Is recruitment on target?
When can I close my study?

- Renew the study as long as data analysis of **identifiable** data is on-going (*Don’t forget publication reviews*)

- When you are completely done with all interventions, follow-up and data analysis, the study should be closed

- If IRB approval of a study expires, no new subjects may be enrolled and all ongoing research activities must stop
UNDERSTANDING WAIVERS
Types of waivers and alterations of IC

• Limited waiver of HIPAA Authorization

• Waiver of consent in its entirety

• Alteration of Consent – One or more of the 8 required elements is eliminated or altered

• Waiver of written (signed) consent—Subject is consented but no signature required. May require providing subjects with an “information sheet”.
Limited waiver of HIPAA Authorization

• Allows for access to existing medical records for the purpose of identifying and making initial contact with potential subjects

• Data collection limited to minimum necessary information to allow identification of potential subjects.

• Records must be destroyed for all subjects who decline participation. All other subjects must sign a HIPAA Authorization form.

A “full” waiver of HIPPA is generally requested along with a waiver of informed consent (e.g., retrospective data collection).
B.2. Protected Health Information (PHI)  
Reference Id: 138148

Protected Health Information (PHI) is any identifiable information about the subject’s health that relates to their participation in this research and is obtained from sources other than the subject, such as medical records, health care providers, insurance plans, etc. [more]

1. Are you requesting a limited waiver of HIPAA authorization?  
If you need to access Protected Health Information (PHI) to identify potential subjects who will then be contacted, you will need a limited waiver of HIPAA authorization [see SOP 29.3]. This does not apply to situations where you will never contact subjects directly (e.g., retrospective chart review), in which case you should request a full waiver under section D. *

- Yes  
- No

Will you access the records of 50 or more patients under this limited waiver? *  

- Yes  
- No

If you access the records of fewer than 50 patients under this waiver, submit a copy of your IRB approval letter and a completed Research Disclosure Form to Health Information Management (HIM). Do not submit this information to the IRB. For additional information about this process, you should contact HIM directly at 595-5691 or 986-1255.

Please provide a response to each of the following questions:

Under this limited waiver, you are allowed to access and use only the minimum amount of PHI necessary to review eligibility criteria and contact potential subjects. Describe the information you are planning to collect for this purpose *

Describe the specific data elements you will need to identify potential subjects: e.g., name, diagnosis, date of treatment, age, contact information.

Describe how confidentiality/privacy will be protected prior to ascertaining the patient’s willingness to participate *

HOW WILL PRIVACY BE PROTECTED BEFORE SUBJECT IS CONTACTED FOR PARTICIPATION: e.g., storing recruitment list in a secure manner

Describe when and how you will destroy the contact information if an individual declines participation *

IF POTENTIAL PARTICIPANT SAYS NO OR CAN’T BE CONTACTED, WHAT WILL YOU DO WITH CONTACT INFORMATION?
Waiver or alteration of elements of IC

Under 45 CFR 46.116(d) the IRB may waive the requirement for obtaining informed consent or approve a consent procedure that leaves out or alters some or all of the elements of informed consent, provided that the IRB finds and documents that all of the following four criteria are met:

• the research involves no more than minimal risk to the subjects;

• the waiver or alteration will not adversely affect the rights and welfare of the subjects;

• the research could not practicably be carried out without the waiver or alteration; and,

• whenever appropriate, the subjects will be provided with additional pertinent information after participation.
The default is for subjects to give informed consent. A waiver might be requested for research involving only existing data or information. More rarely, it might be requested when the research design requires withholding some study details at the outset (e.g., behavior deception). In limited circumstances, parental permission may be waived. This section should also be completed for a waiver of HIPAA because research involves Protected Health Information (PHI) subject to HIPAA regulation, such as patient records.

1. Are you requesting any of the following:

- [ ] a waiver of informed consent in its entirety
- [ ] a waiver or alteration of some of the elements of informed consent
- [ ] a waiver of HIPAA authorization (if you are accessing patient records for this research, you must also request a waiver of HIPAA authorization)

Describe which elements you wish to waive or alter

Tips and Techniques on using the HTML Editor

Will you access the records of 50 or more patients under this waiver? *

- [ ] Yes
- [ ] No
Provide explanation supporting request for waiver of IC or elements of IC

To justify a waiver of the requirement for informed consent, you must affirm, by checking each of the following items that apply to this study. Provide a brief explanation.

<table>
<thead>
<tr>
<th>Item</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The research involves no greater than minimal risk to subjects or to their privacy</td>
<td></td>
</tr>
<tr>
<td>The waiver will not adversely affect the rights and welfare of subjects (Consider the right of privacy and possible risk of breach of confidentiality in light of the information you wish to gather.)</td>
<td></td>
</tr>
<tr>
<td>The research would be impracticable to conduct without the waiver</td>
<td></td>
</tr>
<tr>
<td>When appropriate, there are plans to provide subjects with pertinent information after their participation is over (e.g., Will you provide details withheld during consent, or tell subjects if you found information with direct clinical relevance? This may be an uncommon scenario.)</td>
<td></td>
</tr>
<tr>
<td>The risk to privacy is reasonable in relation to the importance of the knowledge to be gained</td>
<td></td>
</tr>
</tbody>
</table>
Waiver of written (signed) consent

Federal regulations allow the IRB to waive the requirement for written consent for some or all subjects if it finds either:

- That the only record linking the subject and the research would be the consent document AND the principal risk would be potential harm resulting from a breach of confidentiality.

  OR

- That the research presents no more than minimal risk of harm to subjects AND involves no procedures for which written consent is normally required outside of the research context.
The default is for subjects to sign a written document that contains all the elements of informed consent. Under limited circumstances, the requirement for a signed consent form may be waived by the IRB. For example, this might occur for phone or internet surveys, when a signed consent form is either impractical or unnecessary, or in circumstances where a signed consent form creates a risk for the subject.

1. Are you requesting a waiver of any aspect of written (signed) documentation? *
   - [ ] Yes
   - [ ] No

Choose which of the following consent approaches apply and attach the relevant document: *

- [ ] Full consent form minus the signature lines
- [ ] You will be provided with a system built consent form when you reach the Consent Form Module
Provide explanation supporting request for waiver of written documentation

Choose which one of the following justifies the waiver of written documentation:

- The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., study topic is sensitive so that public knowledge of participation could be damaging). Participants should be asked whether they want documentation linking them with the research and the participants’ wishes will govern whether they sign the form. Note: This justification cannot be used in FDA-regulated research.
  
  Explain

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (e.g., many phone or mail surveys, “man in the street” interviews, etc.).
  
  Explain

If your request for a waiver of written documentation applies to some but not all of your subject groups and/or consent forms, please describe and justify
UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS (UPIRSO) & OTHER REPORTABLE EVENTS

Call Jeanne Lovmo with any questions:
919-843-8806
Lovmo@unc.edu
Why does the IRB care?

- Belmont Principle: Respect for Persons
- Need subjects for studies
- Learning what doesn’t work is a valuable lesson
- IRB responsible to monitor risks
Reporting Problems to the IRB

- Federal regulations require prompt reporting to the Institutional Review Board (IRB), appropriate institutional officials, sponsor, coordinating center, and the appropriate regulatory agency representative(s):

  All unanticipated problems involving risks to subjects or others, or that compromise the integrity of the research data, occurring in the course of a subject’s participation in a research study.

(45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)).
UPIRTSO or UP

- **UPIRTSO** = **U**nanticipated **P**roblems **I**nvolving **R**isk to **S**ubjects or **O**thers

- **UP** = **U**nanticipated **P**roblems

“Include(s) any incident, experience, or outcome that meets all of the following criteria:

- **Unexpected** – event, severity or frequency
  - As described in the protocol &/or consent and
  - Found in the study population

- **Related or possibly related** to the research

- Places subjects or others at a **greater risk of harm** that was previously known or recognized—including physical psychological, economic or social harm.
Adverse Event (AE)

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom, or disease, temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research.
From OHRP Guidance

Under 45 CFR part 46: Do not report A; Report B and C.

Vast majority of AEs are NOT REPORTABLE

Small proportion of AEs are UPs

REPORTABLE UPs include “events” that are NOT AEs
Most AEs are not UPIRSOs

- AEs that are expected in terms of specificity, severity, and frequency (e.g., described in the protocol, Investigator Brochure, the literature, or the consent form) are not UPIRSOs.

- AEs that are unrelated to the research or there is simply insufficient information to address causality are not UPIRSOs.

- AEs that do not place subjects at greater risk of harm than was considered by the IRB when it approved the research are not UPIRSOs.
Is the Adverse Event........

1. Unexpected?

2. Related or possibly related to participation in the research?

3. Place subject or others at greater risk than previously known or expected?
1. **Unexpected Problem Involving Risks to Subjects or Others (UPIRISO)**

Federal guidance defines as any incident, experience, or outcome that **meets all of the following criteria:**

1. **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. **Related or possibly related** to a subject’s participation in the research; and

3. Suggests that the research **places subjects or others at a greater risk of harm** (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.
2. Related or possibly related to participation in the research?

- Is the adverse event caused by:
  - Study procedures,
  - Underlying disease, disorder or condition of the subject, or
  - Other circumstances unrelated to the research or underlying disease, disorder or condition of the subject.
3. Place subject or others at greater risk than previously known or expected?

- OHRP defines *serious adverse event* as one that:
  - Results in death,
  - Is life-threatening
  - Results in inpatient hospitalization or prolongations of existing hospitalization
  - Results in disability/incapacity
  - Results in congenital anomaly/birth defect or
  - Based on medical judgment event may jeopardize subject’s health
Serious Adverse Event (SAE)

1. Death
2. Life-threatening
3. Hospitalization (initial or prolonged)
4. Disability or Permanent Damage
5. Congenital Anomaly/Birth Defect
6. Required Intervention to Prevent Permanent Impairment or Damage (Devices)
7. Other Serious Important Medical Events
If the answer to all 3 is YES, then…….
According to federal guidance, “unanticipated problems involving risks to subjects or others” warrant consideration of:

- Substantive changes to the protocol or informed consent process/document;

  Or

- Corrective actions in order to protect the safety, rights and welfare of subjects.
Reporting Timeframes

- UPIRSOs that are serious in nature should be reported to the IRB using the on-line system **ASAP, but no later than one week**

- All other UPIRSOs should be reported to the IRB using the on-line system **ASAP, but no later than two weeks.**
Reporting Timelines

**Protocol Violations** should be reported to the IRB within one (1) week of the investigator becoming aware of the event using the same online reporting mechanism used to report UPs.

**Protocol Deviations** should be summarized and reported to the IRB at the time of continuing review. Deviations should not be reported individually as they occur.
IND Safety Reports

• Individual IND safety reports from external sites should **not** be reported to the IRB unless accompanied by an aggregate analysis (e.g., DSMB report) that establishes their significance and a corrective action plan that addresses the problem.

• IND safety reports shall be maintained by the Investigator and should be reported in summary (e.g., not individual reports) **to the IRB at the time of continuing review.**
Data Safety Monitoring Boards (DSMB) Reports

- Some reports from a DSMB / independent safety monitoring group provide the aggregate analysis of individual IND Safety Reports, and if this report establishes their significance, includes a corrective action plan, and meets the criteria for a UPIRSO, it should be reported using the on-line system and changes to the protocol and consent form should be submitted, if applicable.

- Other reports from a DSMB or other independent safety monitoring group should be provided to the IRB as they become available, or at least as often as the study undergoes continuing review.
Pop Quiz
Nausea during chemotherapy treatment administered at UNC hospitals

Q1: Did the event occur at a site for which UNC IRB has direct oversight?

Q2: Was the event unexpected?
Nausea during chemotherapy treatment administered at UNC hospitals

Q1: Did the event occur at a site for which UNC IRB has direct oversight?  YES

Q2: Was the event unexpected?  NO

The event IS NOT Reportable
Sudden death during chemotherapy treatment administered at UNC Hospitals

Q1: Did the event occur at a site for which UNC IRB has direct oversight?

Q2: Was the event unexpected?

Q3: Was the event related or possibly related to the research?
Sudden death during chemotherapy treatment administered at UNC Hospitals

Q1: Did the event occur at a site for which UNC IRB has direct oversight?  YES

Q2: Was the event unexpected?  YES

Q3: Was the event related or possibly related to the research?  YES

The event IS Reportable
Severe psychological stress from completing a survey on risk-prone behaviors as part of UNC study

Q1: Did the event occur at a site for which UNC IRB has direct oversight?

Q2: Was the event unexpected?

Q3: Was the event related or possibly related to the research?
Severe psychological stress from completing a survey on risk-prone behaviors

Q1: Did the event occur at a site for which UNC IRB has direct oversight?  YES

Q2: Was the event unexpected?  YES

Q3: Was the event related or possibly related to the research?  YES

This event IS Reportable using the on-line system
Subject enrolled at UNC, faints during a blood draw

Q1: Did the event occur at a site for which UNC IRB has direct oversight?

Q2: Was the event unexpected?
Fainting during blood draw

Q1: Did the event occur at a site for which UNC IRB has direct oversight?  YES

Q2: Was the event unexpected?  NO

This event IS NOT Reportable
Sponsor letter that provides the findings of interim review identifying previously unrecognized risks.

Q1: Did the event occur at a site for which UNC IRB has direct oversight?

Q2: Has a determination been made by the Sponsor, CC, DSMB/DMC, etc., that the event meets criteria for UPIRSO?
Sponsor letter that provides the findings of interim review identifying previously unrecognized risks.

Q1: Did the event occur at a site for which UNC IRB has direct oversight? **NO**

Q2: Has a determination been made by the Sponsor, CC, DSMB/DMC, etc., that the event meets criteria for UPIRSO? **YES**

The event **IS** an **UPIRSO**, and therefore, **IS** Reportable to the UNC IRB using the on-line system (and submit changes to protocol or consent form, if applicable).
UNC researcher loses research laptop

Q1: Did the event occur at a site for which UNC IRB has direct oversight?

Q2: Was the event unexpected?

Q3: Was the event related or possibly related to the research?
Lost laptop used for research study

Q1: Did the event occur at a site for which UNC IRB has direct oversight?  YES

Q2: Was the event unexpected?  YES

Q3: Was the event related or possibly related to the research?  YES

The event IS Reportable using the on-line system
Protocol Violations and Deviations

**Protocol Violations** are a variance from the study protocol that:

- Has harmed or increased the risk of harm to one or more research subjects.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

**Protocol Deviations** are a variance from the study protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).
Examples of Protocol Violations

- Proceeding with the research without IRB approval
- Failing to follow IRB-approved procedures
- Implementing any changes without IRB approval
- Enrollment of subjects who do not meet eligibility criteria
- Proceeding with research interventions prior to obtaining written informed consent
- Missed or significantly delayed safety visits or tests.
- Medication errors
Examples of Protocol Deviations

- Performing a planned procedure on a different timetable than previously specified in the research protocol because of an unforeseen disruption such as a subject’s vacation or illness
- Study visits out of window (not affecting subject risk)
- A mechanical failure such as a recording device malfunction
- Late PK specimens
IRB RELIANCE AGREEMENTS

How institutions & individuals not part of an institution can work together
IRB Reliance Agreements

• Formal document that provides a mechanism for an institution engaged in research to delegate IRB review to an independent IRB or an IRB of another institution.

• Used when a trial is conducted at multiple sites, when a participating research entity does not have its own IRB, or when a trial requires specialized IRB expertise.

• Benefits include reduction in duplication and variation, decrease in activation time, and foster collaboration between sites.

Adapted from: http://www.niaid.nih.gov/LabsAndResources/resources/toolkit/Pages/faq.aspx
OHRP Federalwide Assurance (FWA)

Documents an institution’s commitment to comply with federal regulations governing human subjects research.

- Covers all research supported or conducted research involving human subjects

- Requires written formal agreement of compliance from all non-affiliated investigators
Requirements in UNC’s FWA (#4801)

- **The institution** bears full responsibility for ensuring that all human subject research is conducted in accordance with Federal regulations.

- **The IRB** must review and approve or disapprove research involving human subjects according to guidelines set forth in 45 CFR 46.

- **The investigators** acknowledge and accept their responsibility for protecting the rights and welfare of human subjects and for complying with the FWA.

- **NOTE:** Without an FWA, Federally Funded research cannot be done & an FWA can be cancelled by the Office for the Protection of Human Subjects (OHRP)!
3 Types of Agreements

- Inter-institutional agreements (e.g., UNC relies on DUHS, NC State relies on UNC)
- Independent Investigator Agreements (e.g., Bob Smith relies on UNC)
- Central IRB Agreements (e.g., UNC relies on WIRB, UNC relies on the NCI CIRB)
Relying on Central IRBs

• Multicenter, industry-sponsored study, already approved and where the Sponsor/CRO has identified a given central IRB as the IRB of record for the study.

• Use of a central IRB is optional

• You may choose to work with some and not with others or for some kind of studies but not others (e.g., Phase II-IV but not Phase I studies)

• Revised policy allows for the use of 6 central IRBs: 1) WIRB, 2) Quorum, 3) Copernicus, 4) Chesapeake, 5) Sterling and 6) Schulman
IRB Contacts for Reliance Agreements

- For questions about Central IRBs:
  
  **Diane Towle 919-966-0105**

- For questions about all other reliance agreements:
  
  **Jeanne Lovmo 919-966-8146**
NAVIGATING THE IRB APPLICATION & SUBMISSION PROCESS

Call IRB Analysts with questions @ 919-966-3113
Research Equation

Funding + IRB Approval = Study

IRBS submission should be prepared with same care as grant submission.

If done, will have fewer/no stips or delays in approval.
Plan Ahead!

- Your application may be one of 100’s submitted that week
- Pay attention to dates and deadlines (tentative)
- Complete the application as directed
- Provide consents; recruitment materials; and supporting documents
- Familiarize yourself with the “IRB” SOPs
- If you have questions while completing the application or consents, please
  - call 919-966-3113 or
  - email irb_questions@unc.edu
On-line Submissions

- Smart form approach
- Single form builds on itself: NHSR – Exemption – Full application
- System builds consent forms
- Electronic Routing and Approvals
- On-line communication to and from the IRB
- Include a cover memo that explains special circumstances
- On-line Submission Training – web-based videos and printable aids
Routing of IRB Submissions

- PI and/or Study Staff Drafts Application
- Certification by PI (and Faculty Advisor if Student PI)*
- PI's Home Department (Chair or Dept Review Committee)
- Administering Department (if any)
- Oncology PRC or SRS (if relevant)
- IRB

Non-IRB Issues (if any)
Principal Investigator Affirmation

By certifying below, the Principal Investigator affirms the following:

I will personally conduct or supervise this research study. I will ensure that this study is performed in compliance with all applicable laws, regulations and University policies regarding human subjects research. I will obtain IRB approval before making any changes or additions to the project. I will notify the IRB of any other changes in the information provided in this application. I will provide progress reports to the IRB at least annually, or as requested. I will report promptly to the IRB all unanticipated problems or serious adverse events involving risk to human subjects. I will follow the IRB approved consent process for all subjects. I will ensure that all collaborators, students and employees assisting in this research study are informed about these obligations. All information given in this form is accurate and complete.

This study proposes research that has been determined to include Security Level 2 data security requirements. I agree to accept responsibility for managing these risks appropriately in consultation with departmental and/or campus security personnel. The Data Security Requirements addendum can be reviewed here.

If PI is a Student or Trainee Investigator, the Faculty Advisor also certifies the following:

I accept ultimate responsibility for ensuring that this study complies with all the obligations listed above for the PI.
Title of Research Project:
Principal Investigator:

As a member of this research team I understand that I share responsibility for the protection of human subjects. By signing this statement, I am indicating my understanding of these responsibilities and I agree to the following:

• If I am involved with the consent process, I understand that the process is to be conducted as approved by the Institutional Review Board. By means of the consent process, I will ensure that prior to their agreeing to participate, potential subjects will understand that participation is voluntary, will have been given all pertinent details about the study and will have the opportunity to ask questions, and that they will understand what will be asked of them in the conduct of this research.

• I understand that names and any other identifying information and all other information about study participants are completely confidential. I agree not to divulge, publish, or otherwise make known to unauthorized persons or to the public any information obtained in the course of this research project that could identify the persons who participated in the study.

• I understand that any violation as described above may be grounds for disciplinary action, and may include termination of employment.

• I agree to notify my supervisor immediately should I become aware of any violation of ethical principles or regulatory requirements for the protection of human subjects, whether this be on my part or on the part of another person. These might include breach of confidentiality, failure to properly obtain or document informed consent, or deviation from the approved study protocol.

______________________________          ________________       __________________________
Signature           Date          Printed Name

______________________________     ________________    ________________________
Signature of PI          Date                           Printed Name
Department Approvers

By approving, the Home or Administering department affirms that:

- The research is appropriate for the investigator and Department
- The investigator(s) are qualified to conduct the research
- There are adequate resources (financial, support, and facilities) available
- For units that have a local review committee for pre-IRB review, this requirement has been satisfied
- The department supports the application and its review by the IRB
- The department agrees to accept responsibility for managing data security risks in consultation with departmental or campus security personnel
# Research Data Security Grading System

<table>
<thead>
<tr>
<th>Subject IDs</th>
<th>Sensitive Questions</th>
<th>Security Level</th>
<th>Requirements*</th>
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<tbody>
<tr>
<td>---</td>
<td>---</td>
<td>I</td>
<td>Password protection</td>
</tr>
<tr>
<td>YES</td>
<td>---</td>
<td>II</td>
<td>Level I plus secure network</td>
</tr>
<tr>
<td>---</td>
<td>YES</td>
<td>II</td>
<td>Level I plus secure network</td>
</tr>
<tr>
<td>YES</td>
<td>YES</td>
<td>III</td>
<td>Level II plus encryption, vulnerability scans, security audits</td>
</tr>
</tbody>
</table>

* Note that schools and departments will be expected to play a more central role in ensuring security requirements are met. Investigators should consult with IT managers for their units.
IT Expert within the Approving Department
(Department Responsible for the Study)

Level III Data Security Requirements:

Based on the information you've provided, your study will be collecting **sensitive data** that require additional security measures to ensure that they are adequately protected from inadvertent disclosure. Due to the nature of these data, you are required to implement the following security measures on any computer(s) that will store or access information collected for this study. We strongly suggest that you coordinate your efforts in this area with your unit's IT support or IT security personnel.

1. Please provide contact information for the individuals or groups who will provide IT expertise and/or consultation for your study and/or will manage the devices where your study data is stored (IT support within your department or school, research staff with appropriate IT expertise, etc). If unsure, you should consult your department administrator.

Name

Email Address

Phone

Save  Cancel
**Human Research Application for IRB Approval**

IRB Number (00-0000): [ ]  Reference Id: [ ]  Search

**WELCOME TO IRBIS, THE IRB INFORMATION SYSTEM**
The system is designed to be used for all of your interactions with the IRB. Here you can create new applications, modify or update approved studies and view the status of pending submissions. After you select the relevant action from the left hand column, you will be prompted to provide the information needed to complete your submission, including consent forms, as relevant. Your application will be customized to fit the circumstances of your research, depending on your responses as you proceed. The questions are designed to be answered in a sequential order; however, you may use the links in the left column to revisit any portion of the application. Once you have provided the necessary information, your submission will be electronically certified by the principal investigator, routed for department level approvals (when indicated) and then received by the IRB.

For technical assistance in completing/submitting the online application, call the IRBIS Help Desk (919) 966-3685. For substantive questions about IRB reviewer comments, call the IRB Office at (919) 966-3113 and ask to speak with the reviewing IRB coordinator.

[View Sample Application]

Click above to view a sample application with most questions available for review. Your application will differ based on your answers.
1. Is this an interventional study that involves treatment, evaluation or diagnosis of a medical disease or condition? *

- Yes  
- No

If yes, distinguish what is being done specifically for this research from procedures that would be done anyway for clinical care:
Interventions: Research vs. Clinical Care

- **Interventional studies** are those in which the research subjects are assigned by the investigator to a treatment or other intervention, and their outcomes are measured.

- **Observational studies** are those in which individuals are observed and their outcomes are measured by the investigators.

- Answer ‘yes’ to question A.4.A.1 if your study describes both clinical care and activities that are being done for research purposes only.
1. Is this an interventional study that involves treatment, evaluation or diagnosis of a medical disease or condition? *

- Yes  
- No

If yes, distinguish what is being done specifically for this research from procedures that would be done anyway for clinical care:

Tips and Techniques on using the HTML Editor

2. Is this a Clinical Study?
Check YES if this study involves research using human volunteers that is intended to add to medical knowledge. There are two main types of trials and observational studies. Do NOT check yes merely because you are conducting research in a clinical setting or using clinical data.

Click here for additional definition of "Clinical Study"

- Yes  
- No

Will this clinical trial be listed in ClinicalTrials.gov, either by you or the sponsor?

- Yes  
- No

Choose the appropriate Phase designation for this clinical trial.
What is a clinical trial?

• Although there are many definitions of clinical trials, they are generally considered to be biomedical or health-related research studies in human beings that follow a pre-defined protocol.

• Clinicaltrials.gov includes both interventional and observational types of studies.
An agent (drug) will be considered investigational if both the following two criteria are met:

1. administration of the agent is part of a protocol that requires IRB approval
2. a subject is required to sign an Informed Consent Form before receiving the agent

Researchers using investigational drugs in studies must register all studies with the IDS Pharmacy.

Documentation of approval or waiver from IDS should be uploaded in your IRB submission.
NAVIGATING THE IRB WEBSITE
OHRE.UNC.EDU

Call IRB Analyst with questions @ 919-966-3113
IRB and Office of Human Research Ethics

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Protecting Human Research Subjects at UNC: An Introduction

Last year, over one million people took part in research studies at UNC-Chapel Hill. Who are these participants, who is studying them and why? Read more...

ANNOUNCEMENTS

March 2, 2015: The Online Submission Guide has been substantially updated and expanded.

CONTACT

CB 7097
Medical School Bldg. 52
105 Mason Farm Road
1) Your responses to **General Information / Screening Questions** will determine the configuration of your application.

2) You will be presented with a substantially abbreviated application if you indicate that your study:
   - does not constitute research (i.e., “No” response to question #1),
   - does not meet the regulatory definition of human subjects research (i.e., “Yes” response to question #1; and “No” response to both questions #2 and #3).

3) Click the gray bars within the **Item List** to access the constituent sections of each part of the abbreviated “NHSR” (Not Human Subjects Research) application.
Upon receipt of your application, the IRB will determine level of review. Most reviews are expedited, i.e., reviewed in-office, on an ongoing basis, by the Chair and selected reviewers. Only those proposals subject to full board review, i.e., by committee, are required to meet submission deadlines (see table, below).

**IRB Committee Meeting Schedules**

- The **Biomedical IRB** consists of four committees, one of which meets on each of the first four Mondays of the month, unless the Monday is a holiday.

- The single **Non-Biomedical IRB** committee meets the second Tuesday of each month.

- New studies requiring dental expertise are reviewed by the Biomedical Committee B (meets second Monday except holidays). Once approved, a renewal or modification of a dental study can often be reviewed by any of the biomedical IRBs.

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### 2015 IRB Committee Meeting Dates and Submission Deadlines*

<table>
<thead>
<tr>
<th>Non-Biomedical</th>
<th>Biomedical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meeting</td>
<td>Deadline*</td>
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</table>
All applications are online at http://irbis.unc.edu. There are a few **ADDITIONAL FORMS** that are not provided online and may be accessed below. As needed, these should be completed and uploaded to your IRB application.

### FOREIGN LANGUAGE CONSENT FORMS

<table>
<thead>
<tr>
<th>Templates for Standard Consent Documents</th>
<th>Biomedical</th>
<th>Non-Biomedical</th>
</tr>
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<tbody>
<tr>
<td>Consent to Participate in a Research Study</td>
<td>Spanish</td>
<td>Spanish</td>
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<tr>
<td>Adult Subjects</td>
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<td></td>
</tr>
<tr>
<td>Parental Permission for a Minor Child to Participate in a Research Study</td>
<td>Spanish</td>
<td>Spanish</td>
</tr>
<tr>
<td>Assent to Participate in a Research Study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONTACT**

CB 7097  
Medical School Bldg. 52  
105 Mason Farm Road  
Chapel Hill, NC 27599-7097  
Ph: 919-966-3113  
Fax: 919-966-7879  
Help/Questions

**QUICK LINKS**

Online Applications  
Ethics Training  
Dates and Deadlines  
SOPs  
Follow us on Twitter:
The documents listed below are commonly needed regulatory or informational documents for the University of North Carolina at Chapel Hill Office of Human Research Ethics (OHRE) and the Institutional Review Boards (IRBs). Also included on this page is information about proposed regulatory reforms, and UNC comments to these proposals. Access to other related documents can be found on our Resources page.

**REGULATORY DOCUMENTS**

- **Standard Operating Procedures (SOP)** — The University of North Carolina at Chapel Hill Human Research Protection Program Standard Operating Procedures (SOP) describes the policies and procedures that govern human subjects research at this University. These are intended for use by IRB chairs and members, the staff of the Office of Human Research Ethics and investigators and research team members.

- **Federal Wide Assurance (FWA)** — The University of North Carolina at Chapel Hill has committed to uphold regulatory and ethical standards through a Federal Wide Assurance (FWA) approved by the federal Office for Human Research Protections (OHRP). Our assurance with OHRP is FWA #4801. OHRP no longer provides paper copies of these agreements. To view our OHRP assurance records, [CLICK HERE](#) for the OHRP database and follow these steps: 1) click the TAB FOR "FWAs"; 2) enter "4801" in the FWA number field; and 3) click the Search button.

- **Statement of Compliance** — The statement of compliance attests that the Institutional Review Boards at the University of North Carolina at Chapel Hill, administered by the Office of Human Research Ethics, are organized and operate according to applicable laws and regulations governing research involving human subjects. [Click here](#) for a statement explaining that IRB approval documents do not carry signatures.

- **IRB Committee Member Rosters** — There are six IRB committees (rosters): Four Biomedical (A, B, C, D); one Non-biomedical (E); and one devoted to review of institutional review board (IRB) applications for all research conducted at University of North Carolina at Chapel Hill and affiliated facilities.
Relying on Central IRBs

REQUESTING RELIANCE ON A CENTRAL IRB (REVISED 2/25/2015)

UNC allows investigators to utilize a Central IRB for industry-sponsored, multi-center, clinical research studies for which one of the following approved Central IRBs have been appointed as the Central IRB by the Sponsor or CRO and the Central IRB has already approved (or is in the process of approving) the study.

- Chesapeake IRB
- Copernicus Group IRB
- Quorum IRB
- Schulman Associates IRB
- Sterling IRB
- Western IRB

The use of a Central IRB is optional; you may wish to rely on an external IRB for some studies (e.g., Phase III) but not others (e.g., Phase I or II) or may choose to work with some Central IRBs but not others.
IRB and Office of Human Research Ethics

Training and Education Resources

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Research Regulation Resources
Non-Governmental Organizations (NGOs)
Newsletters and Additional Materials
Other
IRB Resources

- IRB Staff (see website for listing: http://research.unc.edu/offices/human-research-ethics/)

- Website: IRB and Office of Human Research Ethics - UNC Research

- Telephone: 919-966-3113

- Address: Bolin Creek, 720 Martin Luther King, Jr. Blvd, CB # 7097 Second Floor

- Education Programs
  - http://www.hhs.gov/ohrp/
  - https://www.youtube.com/watch?v=hsUS0k3le_g&list=SP5965CB14C2506914&index=8
IRB Essentials

1. Good people sometimes lose sight of the big picture and do bad things.

2. Ethical & Regulatory knowledge is as important to your career as a researcher as is your subject area.

3. Your IRB is your friend, not your enemy, use them early & often.

4. Observe an IRB Meeting; better join the IRB.

5. There is no higher authority to appeal an IRB decision to.

6. The IRB, UNC, Feds can all suspend you &/or your research temporarily or permanently.

7. OHRP or FDA can bar you from research and access to federal dollars temporarily or permanently!

8. The internet means everyone knows what happened forever!
UNC IRB  Top 10 Tips

1. Respect & Protect research subjects from harm. Remember Belmont Report principles: Respect, Beneficence & Justice.

2. Federal Regulations Rule, they can shut your study &/or all research at UNC down.

3. Submit to the IRB BEFORE doing research with human subjects,

4. Submit to the IRB BEFORE implementing protocol changes,

5. Do CITI Training & COI before submitting,

6. Call the Office for Human Research Ethics for help before ….

7. Visit an IRB meeting & Consider joining the IRB,

8. Renew your studies on time,

9. Prepare your IRB submission with the same care you did your grant.

10. Report UPs & Protocol Deviations PROMPTLY!!
Are We all Speaking the Same Language?

Both school’s color is blue, but what shade of blue????
For Additional Information:

Charlotte Coley, MACT, CIP
Education & Training Manager
919) 966-1594
chcoley@unc.edu