# IRB 101

The Office of Human Research Ethics

## Introduction

Many of UNC's scientists study people—their health, behavior, and culture—everything that defines us as being human.

Much of their research looks at health or disease and takes place in our schools of dentistry, medicine, nursing, pharmacy, and public health. But UNC researchers also study human social behavior in such varied fields as education, psychology, and social work, just to name a few.

## Who does UNC study?

The people our scientists study are called "human subjects," and over one million took part in more than 5300 different research studies at UNC-Chapel Hill last year!

Each of these human subjects is a volunteer. Some are reimbursed for their travel, parking, lost time to take part in research. But most receive nothing except the satisfaction of helping us learn more about ourselves.

UNC-Chapel Hill is obligated to minimize risks for human subjects, and we take this obligation seriously. Plus, UNC and individual researchers may face severe consequences if we don't follow federal guidelines for research.

## Institutional Review Boards (IRBs)

Before anyone can take part in human research, each project is carefully reviewed by a federally mandated panel of experts, non-scientists, and community members. This panel is called an "Institutional Review Board," or IRB for short. While it's impossible to remove all risk from research participation, IRBs apply ethical standards and federal regulations to judge the safety and value of research. Unlike other boards, the IRB does not review the science of a study or decide if a study should be funded. Its only job is to protect human research subjects, minimize research risks and ensure that they are informed about the study.

There are six IRBs (A–F) at UNC-Chapel Hill made up of members with the expertise appropriate to the research they review. For instance, studies that involve an investigational new drug require a physician IRB member and at least one non-scientist member present at review. For a cancer-specific drug, an oncologist would weigh in on the research. For a study with a social-behavioral goal, an IRB member with a background in psychology, social work, or a similar content area would be present for review. Each board also includes community members who aren't affiliated with UNC and advocates for

vulnerable populations such as the disabled and the incarcerated. These board members bring in a variety of outside perspectives to help educate and protect the people we study.

**Reviewing Research**

At UNC, each IRB meets once a month to review and discuss their assigned research proposals. At these meetings, the IRB may approve a study, approve pending minor changes, disapprove it, or defer it because essential information is lacking that would allow the IRB to properly review it.

**High Risk vs. No More than Minimal Risk Studies**

Typically, only high-risk research needs full board review. Most research is considered minimal or low-risk and is reviewed by individual IRB Chair or Vice Chair on a rolling basis. More on that later.

**Human Research Protection Programs (HRPPs)**

IRBs are just one part of a larger system of research protections called a Human Research Protection Program, or HRPP. At Chapel Hill, the HRPP is administered by the Office of Human Research Ethics, or OHRE.

**The Office of Human Research Ethics (OHRE)**

OHRE is responsible for ensuring the ethical and equitable treatment of all human subjects in research conducted under the auspices of UNC. The research may be externally funded, funded from internal sources, or conducted without direct funding. The office is made up of research analysts, administrators, educators, compliance experts and support staff.

Researchers and IRB members will most typically collaborate with IRB analysts. Analysts are like field guides for researchers. They help navigate application and consent forms; they independently apply and interpret relevant state and federal laws, and they engage necessary departments at UNC such as the Office of Clinical Trials or the Conflict of Interest Office.

**Standard Operating Procedures (SOPs)**

OHRE also maintains UNC's Standard Operating Procedures, or SOPs, for Human Subjects Research. The SOPs define the HRPP's mission, organizational authority, ethical principles, and describe the processes UNC will use to follow federal guidelines for research...and that's just the tip of the iceberg. SOPs can be detailed and complex. Researchers, IRB members, and OHRE staffers (among others) interpret and apply and debate these SOPs every day. Check out OHRE's website for a full list of the SOPs at UNC.

OHRE is a critical part of the research approval process, but the IRBs decide whether to approve research. If an IRB disapproves a study, nobody else at the University can overturn their decision!

If this presentation does nothing else, I hope it demystifies the research approval process. The IRB is often seen as a mysterious Black Hole. Research proposals get sucked in. After that, who knows? How are decisions made?

First, we'll talk about the foundational definitions and regulations that guide an IRB's decision making, overview the IRB process at UNC, and highlight some landmark cases where human subject protections failed.

**Key Definitions**

Let's begin our discussion with two key definitions in The Federal Policy for the Protection of Human Subjects (often referred to as the Revised Common Rule) that frame the regulations. What is research and what is a human subject?

Research is defined as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." For instance, studies that use test subjects or their biospecimens for new devices, products, or drugs would be considered research and are subject to IRB review.

A human subject is "a living individual about whom an investigator conducting research:

(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
(ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens."

If a project does not study human subjects and is not defined as research using the federal definitions, then the project is not Human Subjects Research and is not under the jurisdiction of the IRB. For instance, according to the Revised Common Rule, public health surveillance activities such as COVID testing and tracking are not human subject research and are not within the IRB's jurisdiction.

**The Risk-to-Benefit Ratio**

When reviewing research, the IRB will ask "does the research pose a risk to subjects?" What types of risk are involved? Physical risk from taking an experimental drug? Criminal or civil risk by reporting potentially illegal activities? What about damage to financial standing, employability or reputation?

The National Commission of 1979 says that risk is not just the possibility of harm; but the magnitude and probability of possible harm. How serious are the risks? How likely are they?

Once the researcher and IRB have identified all possible risks to the best of their ability, the IRB will ask: "Do the potential benefits justify the risk?" Has the risk been minimized as much as possible? What specifically are the benefits, if any? Will the study's subjects benefit directly from the research – such as terminal cancer patients trying an untested treatment? Or will the benefits advance scientific knowledge in a way that would not be possible outside the research proposed, to be enjoyed by future patients?

One quick note, if subjects are paid to participate, the Federal Regulations and the IRB will not consider payment a benefit. The IRB will also consider if any payment offered could be coercive and encourage potential subjects to enroll in a study they would otherwise not have joined.

As the risk increases so does the number of those involved in the review, and the amount of time spent on review.

**Exempt and Expedited Review**

If an IRB determines that the research places subjects at no more than minimal risk, meaning the risk one experiences in daily living, the IRB may conduct an exempt or expedited review. These reviews are done in the IRB office on an ongoing basis. There are no submission deadlines. If exempt or expedited, the study is reviewed in about 10-16 days by an IRB Chair or designee. Exempt Review is for studies that fall into an exempt category:

1. Normal educational practices in established educational settings
2. Educational tests, surveys, interviews, or observation of public behavior -unless identified & sensitive**
3. Benign Behavioral Interventions
4. Research using secondary data and/or biospecimens (includes medical records)
5. Evaluation of public benefit services
6. Taste and food quality evaluation and consumer acceptance studies

It's important to note that "exempt" does not mean completely exempt from review. It just means that the study is exempt from review of all criteria for approval.

**Full Board Review**

If the risk is greater than minimal risk, full board review is required. The same holds for studies that do not fall into one of the exempt categories but do meet one of the nine expedited categories. These studies will take several weeks or months to review. More than

minimal risk studies must be referred for full board review at one of the 6 UNC IRBs that each meet monthly. Note that most FDA studies require full board review.

**Minimum Criteria for IRB Approval**

The Federal Regulations include the following list of the minimum criteria for approval that the IRB must use to evaluate all submissions or action items submitted to the IRB for review.

1. Risks are Minimized
2. Favorable Risk to Benefit Assessment
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 Population

The U.S. Department of Health & Human Services, Office for Human Research Protections (OHRP) has a series of flowcharts to help decide if you are doing research, is it human subject review, exempt, expeditable, etc.

What is the purpose of the work? Is it research designed to contribute to generalizable knowledge with intent of publishing or presenting at a national forum? Or is the work to be used for internal assessment and improvement? For instance, quality assurance and quality improvements are often not considered research, but they may be in some instances. Should an activity that has been focused on internal processes at UNC become something that could be generalized and shared with other organizations? At that point you should submit to the IRB for review and approval. We won't have time to go through all the charts, but they're worth looking at.

**Submitting to the IRB at UNC**

For guidance on preparing and submitting to the IRB at UNC, go to OHRE's home page and look at the left margin menus. UNC uses an electronic submission system (IRBIS) that provides options for abbreviated specific submission forms for several types of study considerations. The online submission guide has step-by-step directions and screen shots of IRBIS.

Once you have completed your IRBIS submission and the PI signs off on it. It does not immediately appear in the IRB in box. This slide shows the additional steps and reviews a study passes through before arriving at the IRB. Depending on the study design pre-IRB steps may include advisors, departmental review, Biosafety, Radiation Safety, Cancer Review, etc.

## Federal Regulations: The Belmont Report

So, how does an IRB calculate risk to decide how a study is reviewed? To determine the risk to benefit ratio, the IRB will apply the principles established in the Belmont Report: Respect for Persons, Beneficence and Justice.

Respect for persons establishes two ethical convictions:

1. That people are autonomous. They may choose to join or decline a study based on full knowledge of the risks and rewards and may leave a study at any time without penalty. We call this informed consent.
2. If a person lacks autonomy, such as children, the incapacitated, or the imprisoned, they are entitled to additional protections as appropriate for their situation.

We already talked about beneficence. A proposed research study needs to provide a direct benefit to its subjects or to science to be permissible. No potential benefits means no research.

Finally, Justice. Here we ask, "Who ought to receive the benefits of research and who will bear its burdens?" Historically, the most vulnerable populations, such as minorities, the economically disadvantaged, and the imprisoned have borne the weight of research without receiving its benefits.

## Historical Examples that Inspired Modern Regulations

Regulations and guidelines are often written in response to past ethical lapses. For instance, the Nuremberg Code, which outlines ten ethical principles for human research, was written in response to cruel medical experiments performed by Nazi researchers on unwilling prisoners. The National Research Act and the Belmont Report itself were written after the US Public Health Service's now-infamous Syphilis Study at Tuskegee, which used disadvantaged, rural black men to study the untreated course of a disease that effected the entire population. These subjects were deprived of effective treatment in order not to interrupt the project and the study operated without its subjects' informed consent.

In 1999, 18-year-old Jesse Gelsinger died while participating in an early gene therapy trial at the University of Pennsylvania. Jesse wasn't the first subject in the trial nor the first to experience adverse events that were not reported to the IRB. Had they reported the earlier adverse events; perhaps the study would have been revised or stopped before Jesse joined the study.

## Conflicts of Interest

Note the 2008 article from the PI and his summary of lessons learned from study.

1. The clinical protocol is a contract with the research subjects & regulatory agencies that *must* be strictly & literally adhered to.
2. If you think about reporting—then do so!
3. It is very difficult to manage real or perceived financial conflicts of interest in clinical trials.
4. Informed consent may require objective third-party participation.

Plus, the lead PI was the founder and a 30% share owner of a spin off company that had the patent on the adenovirus vector used in the trial. UPenn held a 5% stake. This information was not shared with the subjects in the informed consent for the study. Because of this lack of reporting, the current Conflict of Interest system was created.

Unfortunately, history is full of examples of unethical research. For now, let's get back to the IRB.

**Continuing Review**

Once a project is approved, it cannot be altered without additional review and approval from the IRB. The researchers may only do what is included in the proposal. If the researcher or sponsor must make changes, then those changes must be approved by the IRB before implementation. Unless the change is for safety reasons to protect subjects.

There are limits to the IRB's approval as well. The maximum approval period is one year; but based on the risk level of the study, the IRB can set it to less time or to match a study milestone.

Once the IRB approves a study, the researcher operates on the honor system. The IRB expects researchers are going to conduct their study as outlined in their submission and will inform the IRB prior to any changes to that research plan, and any adverse events that happen during the course of the study.

**Summary**

In this presentation, we've detailed the IRB's review process at UNC, discussed some foundational regulations that guide their decision making, and highlighted some landmark cases where human subject protections failed.

**Next Steps**

Now, let's talk about some possible next steps to continue learning about human research subjects' protection.

First, as a UNC employee, you are welcome to observe an IRB meeting. Check out OHRE's website for a full list of upcoming meetings. Email the IRB you're interested in (A-F) and give them a few dates that work with your schedule. They'll put you on the calendar.

You'll be asked to sign a confidentiality agreement before you attend your IRB meeting. You cannot share any information about the studies under review.

Next, check out this list of resources that you may find helpful.

OHRE's website has an overview of the IRB review process, a section for frequently asked questions, and pages for guidance on common topics such as IRBIS, Reliance Agreements, and required CITI training for researchers. OHRP's website also has some helpful training information.

If you want to dive deep, visit UNC's library to access Institutional Review Board: Management and Function. IRB staff have relied on it for many years, and you may find it helpful too. And, at 1,000 pages long, it probably has the information you need.

Finally, if you still have questions, email irb_questions@unc.edu or call OHRE's office at 919-966-3113.

Thanks for watching!

**Additional Readings**

The Belmont Report (20-25 minutes)
The Nuremberg Code (2-3 minutes)
The Syphilis Study at Tuskegee Summary (2 minutes)
University of Pennsylvania Gene Therapy Trial Summary (4-5 minutes)

**Additional Viewings**

OHRP - About Research Participation Video Series