Ethical Standards

The Belmont Report
Ethical Principles

Respect for Persons

- Treat individuals as autonomous agents
- Allow people to choose for themselves
- Fundamental right to be left alone
- Extra protections for those with diminished autonomy

Beneficence

- Maximize benefits & minimize risk of harm
- Valid Study Design
- Competent Investigators

Justice

- Burdens and benefits of research should be distributed equitably
- Fair Recruitment
- Unbiased Subject Selection

THE NUREMBERG CODE

1. **The voluntary consent of the human subject is absolutely essential.**

This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment. The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity.

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.

THE NUREMBERG CODE

6. The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.

8. The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him, that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

WHY IS THIS IMPORTANT?

Thinking about ethics will hopefully make you a better researcher, leader, mentor and employee.

It is in your own self-interest to be moral—to make ethical decisions.

Not doing so harms you more than it harms anyone else.

- **Ethical action is not easy, there is no recipe or algorithm, but it can be practiced and it can be taught.**
- **Inaction often may be worse than action.**
- **Acting ethically is a journey, not a destination.**

Jan Boxill, PhD
Former Director, Parr Center for Ethics
Master Lecturer in Philosophy
UNC-CH

Regulatory Standards

CRITERIA FOR IRB APPROVAL

45 CFR 46.111 & 21 CFR 56.111

The IRB must determine that all of the following requirements are satisfied before approval is granted:

1. **Risks to subjects are minimized;**

   - by using sound research design;

   - by using, when appropriate, procedures already being performed for clinical care;

2. **Risks to subjects are reasonable in relation to anticipated benefits and the importance of the knowledge may reasonably be expected to result;**

   - The IRB should consider only those risks & benefits that may result from the research;

   - risks can be physical, legal, economic, social, psychological

3. **Selection of subjects is equitable;**

   - concern for vulnerable populations, for coercion or undue influence of children, prisoners, pregnant women, mentally disabled persons or economically or educationally disadvantaged persons.

CRITERIA FOR IRB APPROVAL

45 CFR 46.111 and 21 CFR 56.111

4. **Informed consent is sought from each prospective subject or the subject's legally authorized representative;**

   - for consent to be legally effective, the subject must have enough information, be able to make/communicate a decision, and understand the consequences of the decision;

5. **Informed consent is appropriately documented;**

6. **The research plan makes adequate provision**

   for monitoring data collected to ensure the safety of subjects;

7. **There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;**

and

8. **When some or all of the subjects are vulnerable to coercion or undue influence,**
   additional safeguards are included to protect a rights and welfare of these subjects.

Definitions

- **Research:** **a systematic investigation, *including development, testing, & evaluation designed to develop or* contribute to generalizable knowledge.**

- **Human subject:** **a *living* individual about whom an investigator*(whether professional or student)* conducting research:**
  - **Obtains data through intervention or interaction with the individual,**
  - **Obtains*, uses, studies, analyzes, or generates* identifiable private information; or**
  - ***Obtains, uses studies, or analyzes biospecimens*.**

Definitions con’t

- ***Clinical trial*** means a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health related outcomes.

- ***An identifiable biospecimen*** **is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.**

Activities NOT Considered Research

(1) Scholarly and journalistic activities (*e.g.*, oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

Activities NOT Considered Research

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

Risk/Benefit Ratio

“Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.”

Institutional Review Board Guidebook, 1993

Minimal Risk

- **45 CFR 46.102(i) defines minimal risk as:**

"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."

- **The IRB makes the determination of risk level.**

- **Minimal risk studies may qualify for exemption or expedited review.**

Types of Risk per 45 CFR 46.101.b.2.I & ii

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**."

Examples:

- **Physical** (e.g. pain, drug side effects, or injury)
- **Psychological** (e.g. emotional distress)
- **Social** (e.g. stigmatization)
- **Economic** (e.g. loss of job—breach of confidentiality that relates to stigma, or workplace competency issues)
- **Legal** (requirements to report some illegal activities, whether the focus of the study, or which emerge without prompting)

Informed Consent Standards

BASIC ELEMENTS OF CONSENT

45 CFR 46.116 & 21 CFR 50.25

A valid consent form must contain the following elements:

1. A statement that the study involves research, an explanation of the purposes of the research , the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

2. A description of potential risks or discomforts to the subject;

3. A description of any benefits to the subject or to others which may reasonably be expected from the research;

4. A disclosure of appropriate alternative procedures;

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

6. For more-than-minimal risk studies, a description of possible compensation & treatment for research-related injury;

7. Who to contact for questions about the research, the subject's rights, or research-related injury; and

8. A statement that participation is voluntary, and refusal to participate or withdrawal from the study at any time will not result in penalty or loss of benefits. **AND**

BASIC ELEMENTS OF CONSENT

45 CFR 46.116 & 21 CFR 50.25 con't.

9. One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

- ***A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or***
- ***A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.***

ADDITIONAL ELEMENTS OF CONSENT *45 CFR 46.116 & 21 CFR 50.25*

When appropriate, the consent form shall also contain the following elements:

1. **A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;**
2. **Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;**
3. **Any additional costs to the subject that may result from participation in the research;**
4. **The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;**
5. **A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;**
6. **The approximate number of subjects involved in the study;**

ADDITIONAL ELEMENTS OF CONSENT *45 CFR 46.116 & 21 CFR 50.25*

7. *A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;*
8. *A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and*
9. *For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).*

REQUIRED ELEMENTS FOR VALID HIPAA AUTHORIZATION

45 CFR 164.508(c)(1) & (2)

Valid HIPAA Authorization must contain the following:

1. **Specific and meaningful description of what information will be used or disclosed.**

2. **Who may use or disclose the information – The name or other specific identification of the person, or class of persons, authorized to make the use or disclosure;**

3. **Specific identification of the person(s) who will receive the information;**

4. **Purpose of use or disclosure – A description of each purpose of the requested use or disclosure.;**

5. **Expiration date or expiration event – An expiration date/expiration event that relates to the individual or the purpose of the use or disclosure. and**

6. **Individual's signature and date – If the authorization is signed by a personal representative, a description of the representative's authority must be provided.**

REQUIRED ELEMENTS FOR VALID HIPAA AUTHORIZATION

45 CFR 164.508(c)(1) (2) (3) & (4)(cont'd)

7. Right to revoke authorization – Outline the right for the individual to revoke their authorization in writing, with an exception that revocation will not apply to information already released in reliance on this authorization. (e.g. in writing to PI)

8. Right to refuse to sign authorization

9. Conditional terms - Ability or inability to condition treatment, payment, enrollment or eligibility for benefits on the authorization and consequences for refusing to sign (e.g., cannot participate in the study).

10. Re-disclosure - Information may be disclosed to others not subject to the Privacy Rule (cannot promise that information will definitely be protected).

11. The authorization must be written in plain language.

12. The covered entity must provide a copy of the signed authorization form to the Individual.

FDA Standards

WHAT ARE THE IRB'S RESPONSIBILITIES WHEN IT RECEIVES A DEVICE STUDY FOR REVIEW?

- IRBs should have standard operating procedures that explain how the IRB makes SR and NSR determinations and that the decision should be documented. FDA considers this determination to be part of the IRB's responsibilities for conducting its initial review of a study. (See 21 CFR 56.108)
- IRBs should make the SR or NSR determination about a study by reviewing relevant information at a convened meeting. This information includes the description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria. The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination.
- An IRB may agree or disagree with the sponsor's initial NSR assessment.
- If the IRB determines the study is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to FDA.
- If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must tell the clinical investigator, and where appropriate, the sponsor. (See 21 CFR 812.66)
- An IRB may approve the study as an SR device study, but the study may not begin until FDA approves the sponsor's IDE application.
- To facilitate the IRB's review of the study, an IRB may ask the sponsor for proof (i.e., a copy of FDA's approval or conditional approval letter) that an SR study has an FDA-approved IDE application.
- The IRB should document its SR/NSR determination in the IRB meeting minutes.

What is a Significant Risk Device Study?

Under 21 CFR 812.3(m), an SR device means an investigational device that:

- Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

- Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

- Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

- Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

What is a Nonsignificant Risk Device Study?

An NSR device study is one that does not meet the definition for an SR device study.

Expedited Category 9

Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Food and Drug Administration (*FDA*) Regulations Related to Human Research

Some studies are also covered by FDA regulations

- Drugs (including nutritional supplements)
- Devices (*including mobile apps, software,*)
- Biologics
- FDA regulations differ from 45 CFR 46 in areas of reporting of adverse events, informed consent waivers, and confidentiality.

Category 9 & FDA

21 CFR 56.109 (c):

(1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form *if it finds 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 the research context; or*

(2) For emergency research per 50.24 criteria

Category 9 & FDA

Remember by definition a study involving a drug (IND) or device (IDE) is always more than minimal risk and waivers do not apply; nor would Cat 9 for continuing review apply.

Child Research

Child Findings

- **§46.404 Research not involving greater than minimal risk.**
  - 1 or 2 parent signature as determined by the IRB

- **§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.**
  - 1 or 2 parent signature as determined by the IRB

- **§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.**
  - 2 parent signature required unless one parent is deceased, unknown, incompetent or not reasonably available or when only one parent has legal responsibility for the care and custody of the child.

- **§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.**
  - 2 parent signature required unless one parent is deceased, unknown, incompetent or not reasonably available or when only one parent has legal responsibility for the care and custody of the child.

HIPAA Standards

18 HIPAA Identifiers:

1. Name
2. Address (Street, City, Zip except for first 3 digits)
3. Dates (all elements directly related to individual; all ages >89)
4. Telephone number
5. FAX number
6. E-mail address
7. Social Security Number
8. Medical Record Number
9. Health Plan Beneficiary Numbers
10. Account Numbers
11. Vehicle identifiers (e.g., serial numbers and license plate numbers)
12. device identifiers and serial numbers
13. URL addresses
14. Biometric identifiers (e.g., finger or voice prints)
15. Full face photographs or comparable images
16. Internet Protocol address numbers
17. Any other unique identifiers
18. Certificate or Professional License Numbers

De-Identification (Safe Harbor)

1. Delete or modify 18 specific items (for subject, relatives, employers)

2. Limited Geocoding (State, part ZIP)

3. Dates are Year only

4. Age > 89 → Age = 90 (Part year age OK)

5. With link-field still requires IRB review

IRB Proceedures

IRB Member Conflict of Interest (*UNC SOP 2102)*

No IRB member may participate in the review of any research project in which they have a COI, except to provide information, as requested. It is the responsibility of each IRB member to disclose any COI related to a study submitted for review and to recuse him/herself from the deliberations and vote by leaving the room.

Conflicts include:

- **Acting as Principal Investigator, Co-Principal Investigator or other key personnel**
- **Personally receiving funding or funded effort from the study, as listed in the study budget**
- **Acting in a supervisory role over the PI of the study,**
- **Being involved in research utilizing a competing technology such that the ability to render an objective assessment could be compromised; or**
- **Being a family member involved in a close personal relationship with a member of the study team (for example, as a spouse or immediate family member)**
- **Involvement in the design, conduct, or reporting of the research with the following exception:**
- **An IRB member who is listed on an IRB protocol as a member of the study's Key Personnel but whose study-related activities are limited to (i) the performance of commercial services for the investigator (or performing other genuinely non-collaborative services meriting neither professional recognition nor publication privileges), while (ii) adhering to commonly recognized professional standards for maintaining privacy and confidentiality, is not considered to have a conflicting interest on this basis.**

IRB Member Conflict of Interest (*UNC SOP 2102) continued*

Conflicts include:

- Supervisory role over the principal investigator of the research.
- A conflict of interest management plan issued by the UNC COI Office overlapping with the research.
- Stock ownership or stock options, equity, or other financial interest related to the research valued at $5,000 or more.
- Personal compensation of $5,000 or more related to the research.
- Proprietary interest related to the research including, but not limited to, a patent, trademark, copyright or licensing agreement.
- Board or executive relationship related to the research, such as an Advisory Board or Board of Directors, regardless of compensation.
- Any other reason for which the member or consultant believes that he or she cannot provide an independent review.

THE *'-ATION"* LIST

A protocol may be deferred if any of the following are required during review by a convened IRB:

Elabor*ation*

Clarific*ation*

Document*ation*

Explan*ation*

Justific*ation*

Modific*ation*

Adapted from Joseph F. Farmer, MD

THE Annotated ‘ATION LIST

Information: In order to [better understand / grasp / make a decision / be informed about the issue], we request additional *information*...

Clarification: Based on what we currently have, [for our purposes / in order to move forward / so we can distinguish] we request additional *clarification* concerning XXX.

Communication: In order to [prove / understand the process of / see the progression of / ensure an ongoing oversight for] XXX, we request additional *communication(s)* regarding YYY.

Explanation: So that we have a [better / deeper / firmer] understanding of XXX, we request [additional / more in depth / more specific / you submit] an *explanation* of YYY.

Justification: So that we can understand [where you’re coming from / what you are referring to / how you plan to support / what components are important to] XXX, we’d like you to provide a *justification* for YYY.

Documentation: So that we can be [better informed / understand the process / have it for the record / see what you are referring to / better reflect what you’ve stated] we’d like additional *documentation* concerning XXX.

Slide Courtesy of Jeremy Block, PhD, MPP

THE Annotated ‘ATION LIST

Modification: In order to [move forward / solve this issue / alleviate this problem / make this better / more closely reflect everyone’s intent] we request a *modification* to XXX.

Authorization: In order to [do what you’ve asked / consider going forward in the direction you propose / make it clear that this course of action is O.K.] we’d like to confirm that there is *authorization* for XXX.

Qualification: So that XXX can be assured to [go forward / have proper protections / be credible] we request that [all the people / all the items important for this] are accompanied by appropriate statements of the varying *qualification(s).*

Demonstration: So that we can [more clearly understand how this works / see what is involved in this / report that we’ve actually seen this / have evidence that this works as described] we’d like to [see / hear / have a report from] a *demonstration* of XXX.

Quantification: In order for us to [better understand / get our heads around the numbers of / crunch on] XXX we’d like a *quantification* of XXX.

Slide Courtesy of Jeremy Block, PhD, MPP

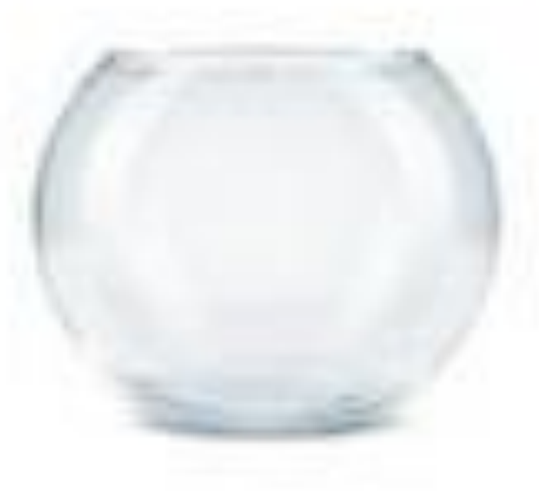
UPs versus Adverse Event

	UP	Adverse Event
Unexpected	√	
Related or possibly related to a subject's participation in the research	√	
Research places subjects or others at a greater risk of harm	√	
Risk listed in consent		√
Happened at another research site		√
Risk listed in consent, but change in severity or frequency	√	√

Continuing Review vs Administrative Review

Continuing Review	Administrative Review (No Continuing Review)
Allowed under Pre-2018 Requirements and under the revised Common Rule	Only allowed for expedited/minimal risk studies under the revised Common Rule
Required of all greater than minimal risk studies	Not allowed for greater than minimal risk studies
Includes expiration date	Includes a due date
Approval for no more than 12 months	Approval until study closure (by PI or OHRE)
Must provide PI a reason if required on a minimal risk study	Given to minimal risk studies unless otherwise communicated to investigator by IRB reviewer

UNC, CH Research Dollars



$1,000,000,000+

TOTAL ANNUAL RESEARCH EXPENDITURES AT UNC-CHAPEL HILL

6th Federal Research Expenditures Nationally

11th Overall Research Expenditures Nationally

6th Nationally Ranked Public Research University