

Ethical & Regulatory Foundation of Human Subjects Research & IRB Review

Human Subjects Protection Program

Fall 2022 HSPP Workshop Series

- 1. Ethical & Regulatory Foundation of Human Subjects Research & IRB Review**
- 2. A Step-by-Step Guide to Successful IRB Submissions (September)**
- 3. Informed Consents & Waivers (October)**
- 4. Let's Talk About Research Data (November)**
- 5. Your Study is Approved, Now What? (December)**

HSPP Training Opportunities:

<https://research.arizona.edu/compliance/human-subjects-protection-program/hssp-training/irb-training-opportunities>

Agenda

- **HSPP & IRB Overview**
- **Historical Background**
- **45 CFR 46**
- **Vulnerable Populations**
- **What Needs IRB Approval?**
- **Resources & References**
- **Discussion**

HSPP & IRB Overview



Human Subjects Protection Program (HSPP)

- Provides **oversight** of research activities involving human subjects.
- We work in **collaboration** with the research community to maintain ethical and compliant research practices at the University of Arizona.
- We provide **guidance** about ethical and regulatory issues to the Institutional Review Board (IRB).
- Provides **administrative support** to the IRB.



Institutional Review Board (IRB)

The IRB is an **Institutional Review Board** made up of medical, scientific, non-scientific, and community members who **protect the rights and welfare** of research participants.

IRB review is based on **Ethical Principles** and it is required by **Regulations**.

Ethical Principles:

- [The Nuremberg Code](#)
- [WMA Declaration of Helsinki](#)
- [The Belmont Report](#)

Federal Regulations:

- [45 CFR 46](#) HHS Protection of Human Subjects in Research
- [21 CFR 50](#) FDA Protection of Human Subjects
- [21 CFR 56](#) FDA Institutional Review Boards

Other:

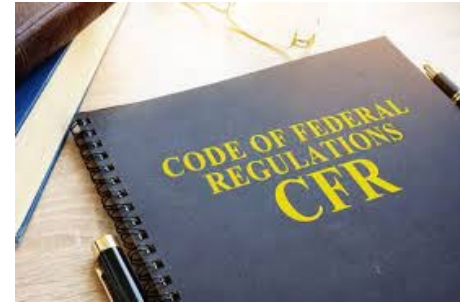
- [ICH GCP Section 3](#) (Clinical Trials)



What is Regulatory?

Merriam-Webster Dictionary Definition:

- relating to regulation
- making or concerned with making regulations



Code of Federal Regulations (CFRs):

- Is a codification of the general and permanent rules published in the Federal Register by the executive departments and agencies of the Federal Government.
- CRFs tell federal agencies and IRB's how to operate.

Regulator:

- A government agency that regulates:
 - Department of Health and Human Services (HHS) Offices & Agencies
 - Office of Human Subjects Protections (OHRP)
 - NIH (45 CFR 46)
 - FDA (21 CFR 50 & 56)

What Does Ethical Mean?



Merriam-Webster Dictionary Definition:

- of or relating to ... *ethical theories*
- involving or expressing moral approval or disapproval ... *ethical judgments*
- conforming to accepted standards of conduct... *ethical behavior*

Ethical Principles:

- The Nuremberg Code
- Declaration of Helsinki
- The Belmont Report



Examples of Unethical Studies

1932 – 1973 Tuskegee Study of untreated SYPHILIS

Researchers looked at the natural course of syphilis in 400 underprivileged African American men in Macon County Alabama. In this study participants had syphilis, but they did not receive treatment for it. When penicillin was found to be effective for treating syphilis in the 1950s, it was withheld from the subjects so researchers could continue to study them.

1946 – 1953 Radioactive Cereal Experiment

Researchers fed cereal tainted with radioactive calcium and iron to more than 70 children at the Fernald School, a state home for mentally disabled children in Massachusetts in order to track the absorption of those nutrients during digestion. To increase participation, the children were told that they were part of a science club.

1963 Jewish Chronic Disease Hospital Study

Researchers at Sloan-Kettering Cancer Research Institute, injected live cancer cells into chronically ill elderly patients at Brooklyn's Jewish Chronic Disease Hospital without their consent. The experiment intended to measure the patients' ability to reject the cells and was not related to their treatment.

1971 San Antonio Contraception Study

A Texas contraception clinic that served a large minority and Hispanic population, conducted a study to evaluate the efficacy of different kinds of female contraceptive pills. The women were not informed that they were in a study and half of them were randomized to placebo. This resulted in a high number of unplanned pregnancies mostly in the placebo arm.

Examples of Unethical Studies

1939 Stuttering Experiment

22 children at a state-run Orphanage in Iowa were subjected to steady harassment, and other negative therapy to try to get them to stutter in order to see if stuttering was a learned behavior induced by psychological pressure.

1955 Wichita Jury Study

Researchers at the University of Chicago wanted to better understand the decision-making process of jurors in criminal trials. They audio taped jury deliberations. The jurors were not told that they were subjects of research or that they were being recorded. The study led to a national discussion about deceit in research and the expectation of privacy.

1961 – 1963 Milgram Study

Stanley Milgram from Yale University conducted a social science study in an attempt to understand the role of obedience to authority. The research used deception about the purpose of the study and procedures. Participants thought they delivered a lethal shock of electricity to another subject (who was an actor), resulting in emotional distress.

1971 Stanford Prison Experiment

Philip Zimbardo from Stanford University conducted a study of the psychology of imprisonment by setting up a mock prison using volunteer college students who were assigned to be prisoners and guards. The student “guards” brutalized the student “prisoners”. The experiment ended up causing psychological harm.

Historical Background



The Nuremberg Trials

(Nov 20, 1945 – Oct 1, 1946)

International Military Tribunal held by the United States, Great Britain, France, and the Soviet Union to hold Nazi leaders accountable for:

- Crimes against peace
- War crimes, and
- **Crimes against humanity**



**Prisoners
Women
Children and
Minority populations**



More information about the Nuremberg Trail from the National WWII Museum:
<https://www.nationalww2museum.org/war/articles/the-nuremberg-trial-and-its-legacy>

The 1947 Nuremberg Code

1. The **voluntary consent** of the human subject is absolutely essential.
2. The experiment should yield **fruitful results for the good of society**.
3. Human research should be founded on the preliminary results **from animal experimentation**.
4. **All unnecessary physical and mental suffering and injury should be avoided**.
5. **No experiment** should be conducted where there is a prior reason to believe that **death or disabling injury** will occur.
6. The **degree of risk** to the subject should never exceed 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. Only sufficiently **qualified persons** should conduct research with humans.
9. The human subject should be at liberty to **stop their participation**.
10. The researcher **must stop the experiment** if it becomes apparent that injury, disability or death is a likely result of continuation.



1953 American Medical Community Response to the Nuremberg Code

- American medical researchers did not respond favorably to the Nuremberg Code; they did not think it applied to them.
- Joseph Gardella, Dean of the Harvard Medical School in 1953, stated “The Nuremberg Code was conceived in reference to Nazi atrocities and was written for the specific purpose of preventing brutal excesses from being committed or excused in the name of science. The code ... is in our opinion not necessarily pertinent to or adequate for the conduct of medical research in the United States.”
- Physician-researchers felt they were adequately governed by the Hippocratic ideal of “Do No Harm.”



WORLD
MEDICAL
ASSOCIATION

1964 Declaration Of Helsinki

- The Declaration of Helsinki was developed in 1964 by the World Medical Association as an international statement of ethical principles to guide medical professionals conducting research involving human subjects.
- Expanded the Nuremberg Code and applied it to research conducted by the medical community.
- Introduced the concept of an independent Committee, which later evolved into the IRB.
- Focuses on two separate categories of clinical research (therapeutic and non-therapeutic), with distinct guidelines for voluntary informed consent.



National Institutes
of Health

1964 NIH Ethics Committee

- NIH Clinical Research Center (CRC) was in charge of overseeing the conduct of clinical research.
- Introduced the idea of a formal ethical review of research at public and private institutions.
- NIH Director James Shannon established a policy that required an ethics committee to review all research funded by U.S. Public Health Service.

1966 BEECHER ARTICLE PUBLISHED IN THE NEW ENGLAND JOURNAL OF MEDICINE

- Dr. Henry Beecher's article titled "Ethics of Clinical Research" cited 22 published studies with serious ethical flaws.
- He wanted to bring attention to abuses done in the name of science.
- His article sparked a debate on research ethics in the U.S.

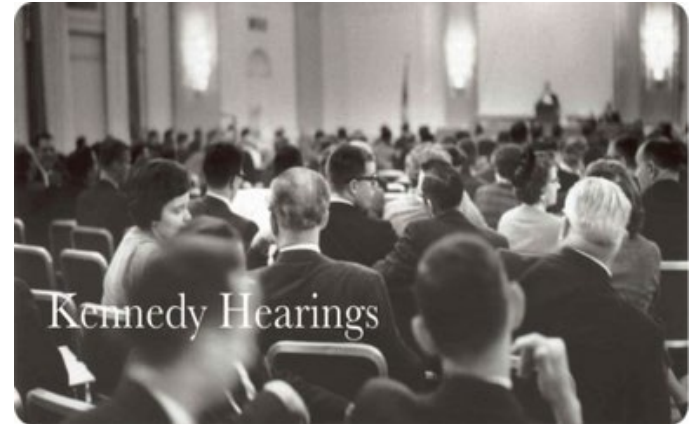


NIH National Library of Medicine:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2566401/pdf/11368058.pdf>

1973 Congressional Hearings on the Quality of Healthcare and Human Experimentation

- In 1973, the Subcommittee on Health of the Committee of Labor and Public Welfare investigated the Tuskegee Syphilis experiment.
- Led by Senator Edward Kennedy, the subcommittee heard testimony from individuals involved in all perspectives of the study.
- Based on these hearings, Congress approved the **National Research Act**, which provided protection of human subjects involved in biomedical and behavioral research.



The National Research Act of 1974

- Established the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research, which was the first national body to officially influence bioethics in the U.S.
- The Act authorizes federal agencies (i.e.; the NIH and FDA) to develop human research regulations.
- Established the concept of IRB review.
- In 1978, identified ethical principles that should govern which was released as the 1979 The Belmont Report.



1979 The Belmont Report

Respect for Persons

Protecting autonomy, having courtesy and respect for individuals as persons, including those who are not autonomous

Beneficence

Maximizing good outcomes for science, humanity, and the individual research participants while avoiding or minimizing unnecessary risk, harm, or wrong

Justice

Ensuring reasonable, non-exploitative, and carefully considered benefits among persons and groups





1981 Common Rule

- The Common Rule regulations are process-oriented and provide definitions for human subjects research as well as the elements of the informed consent.
- In 1981, the US Department of Health and Human Services (DHSS) published a revision of 45 CFR 46 Subpart A, which incorporated the Belmont Report principles.
- It also formally required IRB review and approval of research involving human subjects.
- It also specified IRB composition, procedures, and responsibilities.



1980—1981 FDA Requires IRB Review of Clinical Trials

1980 - FDA issued **21 CFR 50** (Protection of Human Subjects)

1981 - FDA issued **21 CFR 56** (Institutional Review Boards)

- The FDA regulations established requirements for IRB review and informed consent for FDA-regulated clinical trials.
- They also extended human subjects protections to any research study involving FDA regulated products (i.e.; drugs or devices), beyond the HHS regulations, which only apply to federally funded research.

1991 The Common Rule

(45 CFR 46 Part A)



- Prior to 1991, different federal agencies used a variety of policies and procedures to protect human research subjects.
- In 1991 the Federal Policy for the Protection of Human Subjects was published by DHHS and it was adopted as the “Common Rule” by other federal agencies and departments.
- Subpart A was codified in the regulations of 15 federal agencies/departments, to include language that is identical to 45 CFR 46, subpart A.
- In addition, four departments or agencies follow this “Common Rule” by statutory mandate (Department of Homeland Security, Social Security Administration, Office of the Director of National Intelligence, and Central Intelligence Agency).
- All U.S. government agencies, except the FDA, now accept one basic regulatory framework, known as "the Common Rule" (45 CFR 46).

The Common Rule 45 CFR Part 46 Subpart A

Adopted by 18 federal departments & agencies

Department of Agriculture 7 CFR Part 1c	Department of Energy 10 CFR Part 745	National Aeronautics and Space Administration 14 CFR Part 1230
Department of Commerce 15 CFR Part 27	Consumer Product Safety Commission 16 CFR Part 1028	Agency for International Development 22 CFR Part 225
Department of Housing and Urban Development 24 CFR Part 60	Department of Justice 28 CFR Part 46	Department of Defense 32 CFR Part 219
Department of Education 34 CFR Part 97	Department of Veterans Affairs 38 CFR Part 16	Environmental Protection Agency 40 CFR Part 26
Department of Health and Human Services 45 CFR Part 46	National Science Foundation 45 CFR Part 690	Department of Transportation 49 CFR Part 11
Central Intelligence Agency *	Department of Homeland Security*	Social Security Administration*

**Denotes compliance with ALL subparts of 45 CFR part 46, but have not issued the Common Rule in regulations*

Other Notable Dates

1993 NIH required inclusion of Women and Minorities as subjects of clinical research. The policy stated that women and members of minority groups must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

2016 Single IRB Mandate. NIH mandated that all multi-site cooperative research funded by NIH must rely upon ethical review and approval conducted by a single IRB of record. The policy affects non-exempt human subject's research. [45 CFR 46.114 Cooperative Research].



45 CFR 46



Human Subjects Research Regulations **45 CFR 46**

Subpart A: Basic Policy for the Protection of Human Subject (Common Rule).

Subpart B: Additional protections for pregnant women, human fetuses, and neonates.

Subpart C: Additional protections for prisoners.

Subpart D: Additional protections for children.

Subpart E: Requirements for IRB registration (FWA).

IRB Functions & Authority

45 CFR 46.109 IRB Review of Research

- The IRB has the authority to **approve, require modifications** (to secure approval), **or disapprove studies** and all human subjects research related activities.
- The IRB also has the authority to observe or have a third party **observe the consent process and the research**.
- **Conduct Continuing Review (CR)** of research requiring review, appropriate to the degree of risk, not less than once per year for projects reviewed by the convened IRB.

45 CFR 46.113 Suspension or Termination of IRB Approval of Research

- The IRB has the authority to **suspend** or **terminate approval** of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects.

How Does the IRB Protect Human Subjects?

45 CFR 46.111 Criteria for Approval

- (1) Risks are minimized** by using procedures that do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
- (2) Risks to subjects are reasonable in relation to anticipated benefits** the importance of the knowledge expected to be gained.
- (3) Selection of subjects is equitable.**
- (4) Informed consent will be sought** from each prospective subject or the subject's LAR; for children Parental Permission/Assent is obtained.
- (5) Informed consent will be appropriately documented or waived.**
- (6) There are adequate provision for monitoring the data to ensure subject safety.**
- (7) There are adequate provisions to protect the privacy of subjects** and to maintain the **confidentiality of data.**



2018 NEW Common Rule (2018 Requirements)



- The New Common Rule regulations took effect on January 19, 2019.
- Definition of a clinical trial and benign behavioral intervention.
- Increased protections for research data and confidentiality.
- Revised Exempt Categories, with New Exempt categories related to benign behavioral intervention, as well as storage, maintenance and use of identifiable data or biospecimens.
- CR is not required for exempt/minimum risk studies, and research eligible for expedited review or limited IRB review.
- Streamlined consent but with more consent elements (i.e., future use, commercial profit, sharing of results, and whole genome sequencing).

Comparison between the Old (Pre-2018) & New (Post-2018) Common Rule
<https://www.hhs.gov/ohrp/regulations-and-policy/regulations/annotated-2018-requirements/index.html>

Vulnerable Populations

- **Children** (Subpart D)
- **Pregnant women, fetuses and neonates** (Subpart B)
- **Prisoners** (Subpart C)
- **Cognitively impaired** persons (permanent or transient)
- **Anyone vulnerable to coercion or undue influence.**
- **Low socio-economic** persons
- **Students** and **Employees**
- **Patients**
- **Illiterate persons**
- **Undocumented migrants**

45 CFR 46.107 "If an IRB regularly reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as **children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged** persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with these categories of subjects".

UA HSSP Appendices

- Appendix for **Children/Wards**
- Appendix for **Cognitively Impaired Individuals**
- Appendix for **Native American & Indigenous Populations**
- Appendix for **Prisoners**
- Appendix for **Pregnant Women, Neonates, and Fetuses**

HSPF Forms: <https://research.arizona.edu/compliance/human-subjects-protection-program/HSPF-form/forms-index>

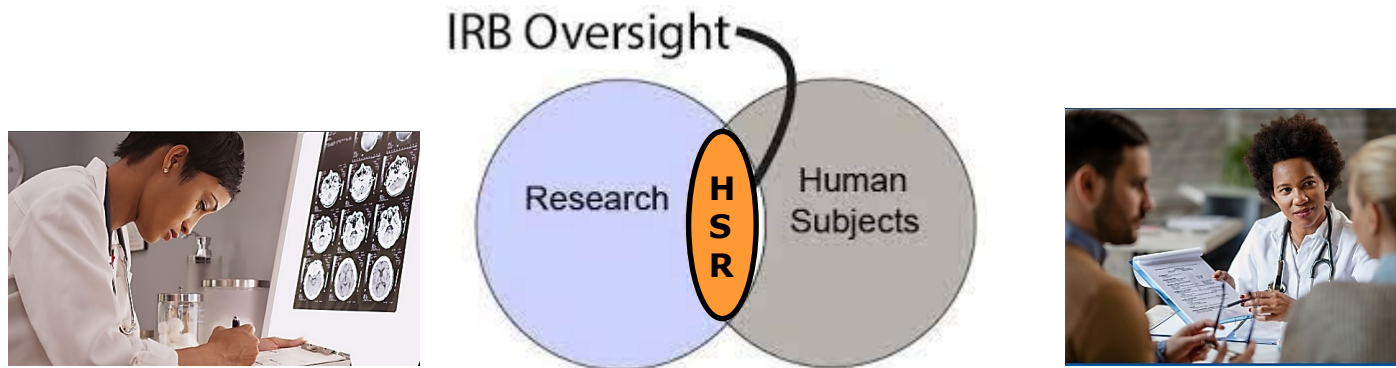
Related UA HSPP Guidance Documents

- [Research Involving Children](#)
- [Research Involving Cognitively Impaired Adults](#)
- [Research Involving Native Americans or Indigenous Populations](#)
- [Research Involving Neonates](#)
- [Research Involving Pregnant Women](#)
- [Research Involving Prisoners](#)

What Needs IRB Approval?



Not every project needs IRB approval



If the activity is **“Research”** or **“Clinical Trial”**
and involves **“Human Subjects”**
the activity requires review and approval by the IRB.

HSPG Guidance: What is Human Research?

<https://research.arizona.edu/sites/default/files/What%20is%20Human%20Research%20v2021-09.pdf>

Definition of Research



HHS 45 CFR 46

Research is defined as a **systematic investigation**, including research development, testing and evaluation, designed to develop or contribute to **generalizable knowledge**.

***UA interprets *generalizable* to mean that results can be applied to the population at large.**

Clinical Trial: 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 intervention on biomedical or behavioral health-related outcomes.

FDA 21 CFR 50

Clinical Trial: An **experiment that involves a test article** administered to one or more humans (except marketed drugs in the course of medical practice).

Test Article: Any drug (including biological product for human use), device, food/color additive, electrical product, or any other article subject to regulation.



Definition of Human Subject



A **human subject** is a **living** individual about whom an investigator (whether professional or student) conducting research:



1) Obtains information or biospecimens through **intervention** or **interaction** with the individual, and uses, studies, or analyzes the information or biospecimens;

OR

2) Obtains, uses, studies, analyzes, or generates **identifiable private information** or **identifiable biospecimens**.

Intervention includes both physical procedures by which information is gathered and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction includes communication or interpersonal contact between investigator and subject.

Identifiable is where the identity of the subject is or may be ascertained by the researcher or will be associated with the information. **The research could involve the use of coded data/specimens.**

Examples of NOT Human Subjects Research

Projects that are not generalizable:

- **Program Evaluations (PE)**
- **Quality Improvement Projects (QI)**
- **Case Reports** (of up to (3) cases describing an interesting treatment, presentation, or outcome)

Activities specifically excluded under the New 2018 Common Rule:

- **Scholarly or journalistic activities, including oral history**, biography, literary criticism, legal research, and historical scholastic activities.
- **National Security Missions**
- **Public Health Surveillance**
- **Criminal Justice Activities**

HSPG Guidance: Case Reports

<https://research.arizona.edu/sites/default/files/Case%20Reports%20v2021-09.pdf>

HSPG Guidance: Quality Improvement (QI) and Program Evaluations (PE)

<https://research.arizona.edu/sites/default/files/What%20is%20Human%20Research%20v2021-09.pdf>

Still Unsure?



The **IRB Protocol for Determination of Human Research** should be used when it is unclear if the project requires IRB approval.

<https://research.arizona.edu/compliance/human-subjects-protection-program/HSPP-form/forms-index>

This form is **required** if the proposed study involves the following activities, and it is unclear whether these activities require IRB review:

- Access to electronic medical records (**EMR**);
- Use or disclosure of Protected Health Information (**PHI**);
- Requests for data or specimens from the Banner Clinical Research Data Warehouse (**CRDW**);
- The project is or will be supported by **federal funds (i.e., NIH)** that involves people;
- The information will be used to support an application to the **FDA** or involves the use of a test article in a human;
- IRB certification for access to materials from **dbGap**; OR
- The project involves **Native American/Alaskan Native or indigenous populations.**

Resources & References





Resources & References

- **HSPP Website:** <https://research.arizona.edu/compliance/human-subjects-protection-program>
- **HSPP Forms:** <https://research.arizona.edu/compliance/human-subjects-protection-program/HSPP-forms>
- **HSPP Guidance Documents:** <https://research.arizona.edu/compliance/human-subjects-protection-program/guidance-researchers>

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HSPD Webpage:

<https://research.arizona.edu/compliance/human-subjects-protection-program>



HSPP Office Hours

HSPP Virtual Office Hours

are held every other Thursday
from 10 am – 11 am.

No registration is required

Use this link to join :

<https://arizona.zoom.us/j/86232995912>

Remaining 2022 Dates

- September 1
- September 15
- September 29
- October 12
- October 27
- November 10
- November 24
- December 8
- December 22



Stay in the Loop



Subscribe to the HSPP listserv:

- Send a blank email to: list@list.arizona.edu
- In the subject line, enter: subscribe UA-IRB Firstname Lastname
- Delete any signature line and/or confidentiality statement that you may have in your e-mail.

Subscription Instructions: [https://it.arizona.edu/documentation/how-
subscribe-and-unsubscribe-list](https://it.arizona.edu/documentation/how-subscribe-and-unsubscribe-list).

Discussion



Some Questions to Consider



1. What is the purpose of Human Subjects Regulations?

The main purpose of the regulations & guidelines is to minimize harm and exploitation in Human Subject's Research.

2. Why do you need IRB approval?

IRB Review and approval is required by Federal Regulations.

Human Subjects Research activities **Can Not Start** before IRB approval.

3. Why do research subjects need to be protected?

Because of past atrocities and unethical research practices, federal regulations require the protection of all research participants.

Extra protections are given to vulnerable populations including children, fetuses, neonates, prisoners, people of diminished capacity, and anyone susceptible to undue influence or coercion.

Comparing & Contrasting the Ethical Codes

1. What do the Ethical Codes have in common?

The purpose of the Ethical Codes and Principles is to protect research participants and to minimize risk.

2. How are the Ethical Codes different?

The Declaration of Helsinki expands the Nuremberg Code

The Belmont Principles are less detailed and more flexible

3. Is there an ethical principle that stands out to you as most important or more important than the others?

Voluntary and fully informed consent is emphasized

Beneficence is important for study design and conduct



Polling

Nuremberg Code	Declaration of Helsinki	The Belmont Report
<ul style="list-style-type: none"> • 10 Codes • Specific statements regarding ethical researcher conduct. • Developed as a result of WWII atrocities. • Above all - Consent must be voluntary. 	<ul style="list-style-type: none"> • Over 32 Paragraphs • Each paragraph is about a specific topic. • Outlines physician responsibilities to prioritize participant health. • Most people relate it to medical research. 	<ul style="list-style-type: none"> • 3 Principles • More Flexible • Can be applied to more complex ethical questions. • UA IRB applies the Belmont Report to all human subject's research.

A summary of important documents in the field of research ethics
<https://pubmed.ncbi.nlm.nih.gov/16192409/>

Applying The Belmont Report Principles

Respect for Persons

- Voluntary informed consent
- Documentation of consent or ICF Waiver
- Parental Permission
- Assent
- LAR signature
- Opportunity to ask questions
- Right to withdraw
- No Coercion
- No Undue Influence
- Extra protections for vulnerable populations

Beneficence

- Research risk justification
- Minimizing risk by incorporating current tools, knowledge & best practices
- Scientific/Peer Review to determine soundness of the protocol.
- Departmental Approval
- Proper qualification and training (CV, CITI, etc.)
- Advisors/Consultants
- Responsible Physicians
- Ancillary Reviews/COI

Justice

- Fair distribution of risks and benefits
- Properly Justified Inclusion/Exclusion
- Recruitment
- Compensation
- No exploitation
- No penalty for withdrawal
- Limit the use of vulnerable populations (children, prisoners, etc.) to research that can't be answered without them.

Questions?

