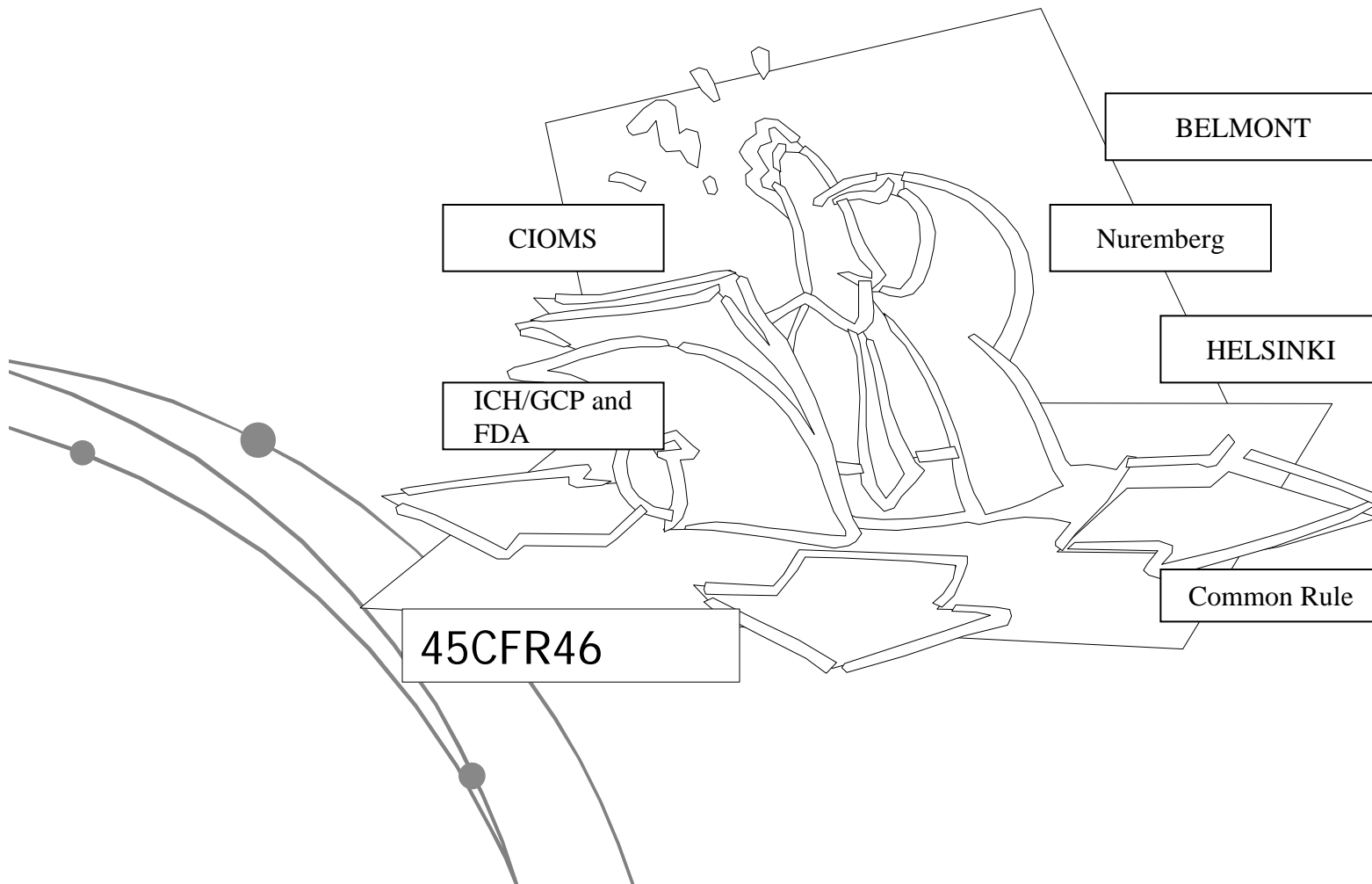


WHICH CODES APPLY TO MY RESEARCH?



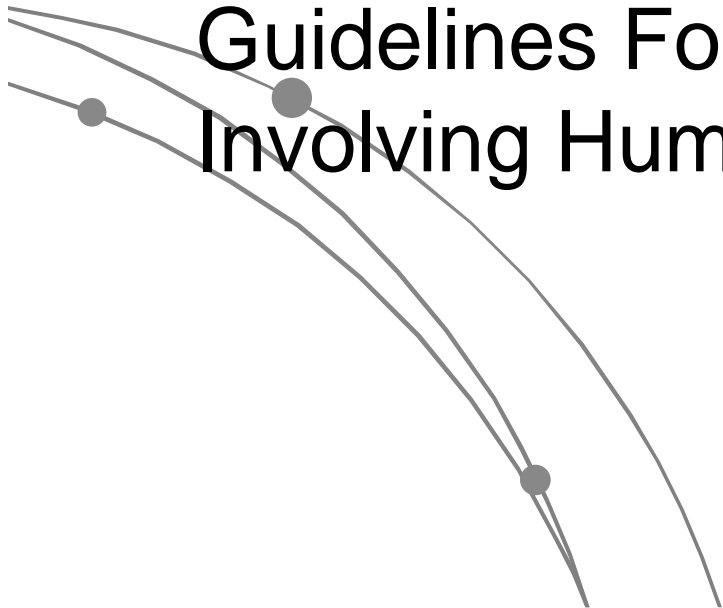
Which codes?

- An NIH-funded investigator is conducting a randomized, placebo controlled study of a new drug for arthritis. She intends to publish the results.

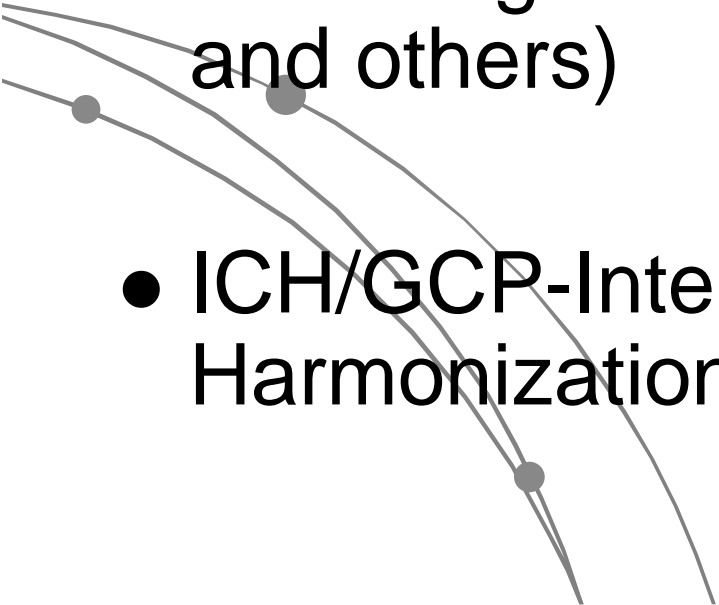
- 
- Which codes should she follow?

Codes of Research Ethics

- The Nuremberg Code
- The Declaration Of Helsinki
- The Belmont Report
- CIOMS/WHO International Ethical Guidelines For Biomedical Research Involving Human Subjects

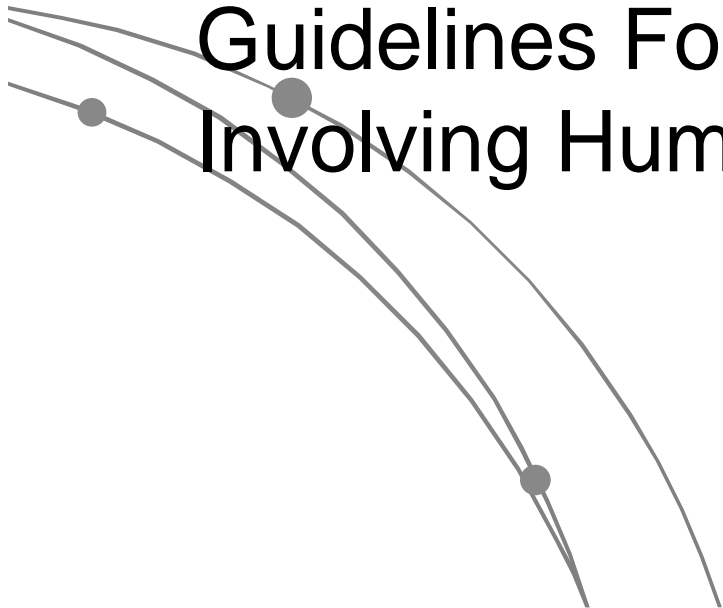


U.S. Federal Regulations and Guidelines

- Title 45 US CFR 46
 - The Common Rule (Subpart A)
 - Subparts B, C, D
 - FDA Regulations (21 US CFR 50 & 56, and others)
 - ICH/GCP-International Conference on Harmonization- Good Clinical Practice
- 

Codes of Research Ethics

- The Nuremberg Code
- The Declaration Of Helsinki
- The Belmont Report
- CIOMS/WHO International Ethical Guidelines For Biomedical Research Involving Human Subjects

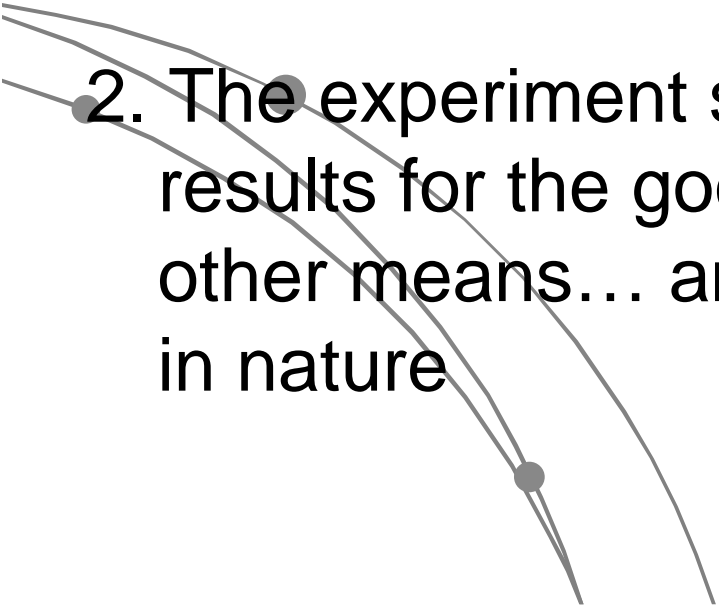


Nuremberg Code 1947

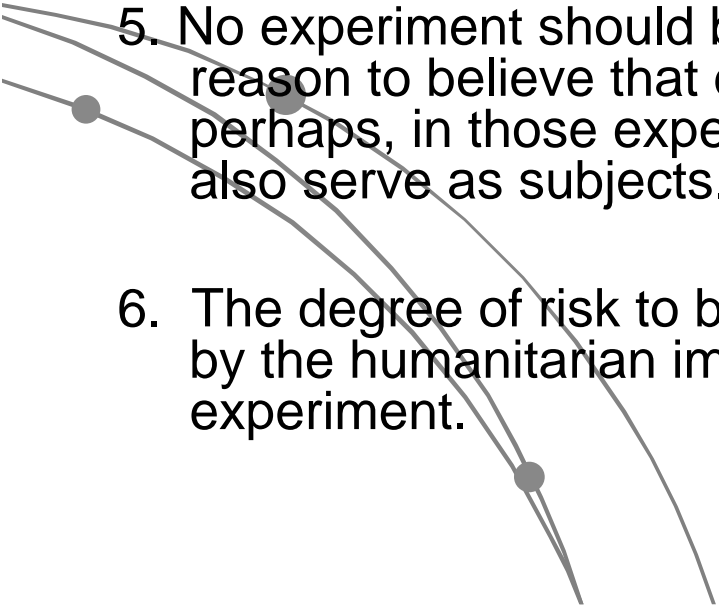
- 10 principles from the Nazi doctor's trial

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

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



Nuremberg Code

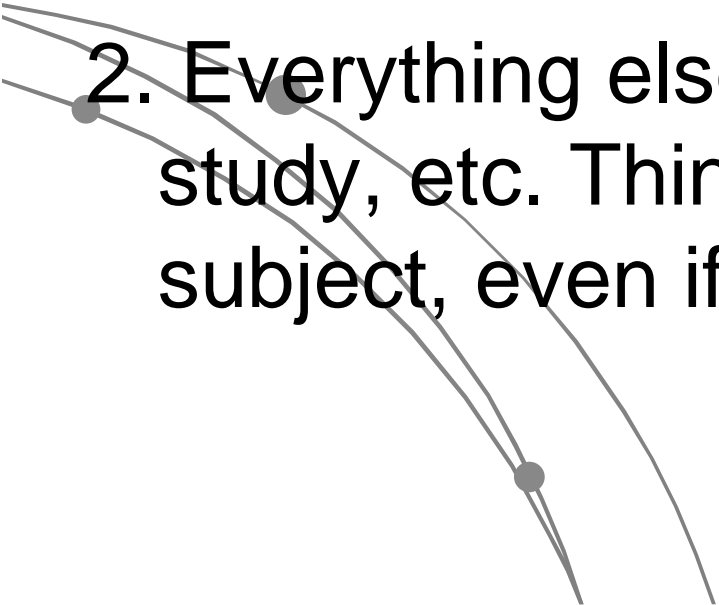
3. ...designed and based on the results of animal experimentation and a knowledge of the natural history of the disease...that the anticipated results will justify the performance of the experiment.
 4. ... conducted as to avoid all unnecessary physical and mental suffering and injury.
 5. No experiment 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.
 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.
- 

Nuremberg Code 1947

- Note two themes:

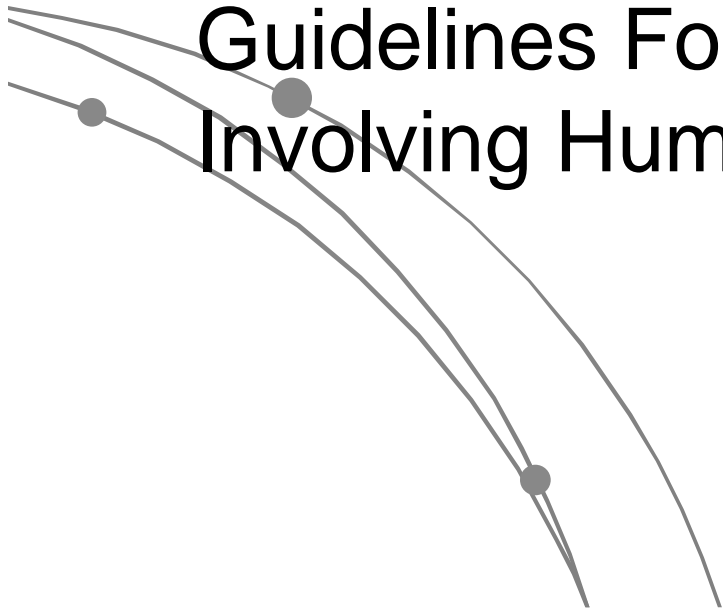
1. Informed Consent !!!!!

2. Everything else—substantive design of the study, etc. Things we won't let happen to a subject, even if they give consent.

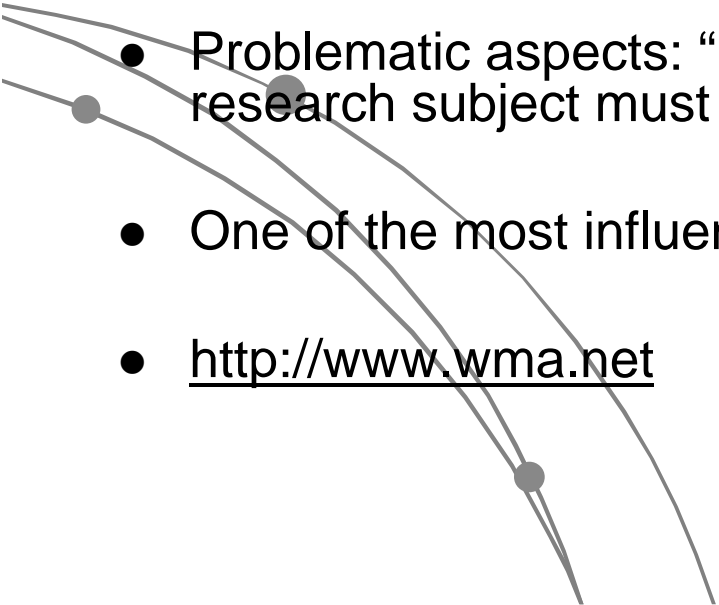


Codes of Research Ethics

- The Nuremberg Code
- The Declaration Of Helsinki
- The Belmont Report
- CIOMS/WHO International Ethical Guidelines For Biomedical Research Involving Human Subjects

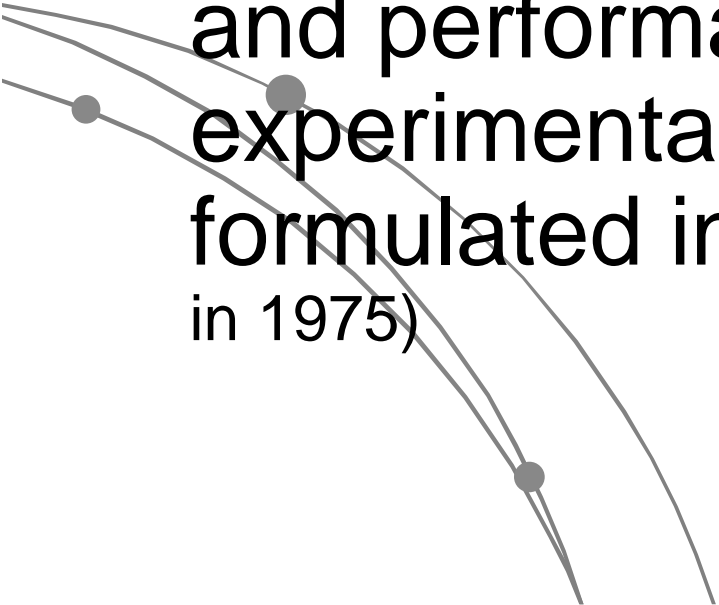


Declaration Of Helsinki

- World Medical Association
 - By physicians for physicians
 - A “living” document revised multiple times (1964, ‘75, ‘83, ‘89, ‘96, 2000, 2008)
 - Problematic aspects: “[In research,] the well-being of the individual research subject must take precedence over all other interests.”
 - One of the most influential documents in research ethics
 - <http://www.wma.net>
- 

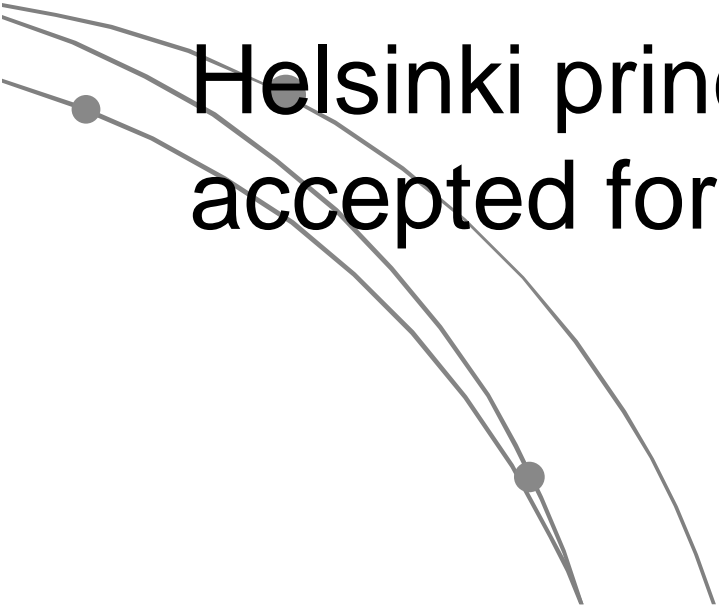
Declaration Of Helsinki

(pre-2000)

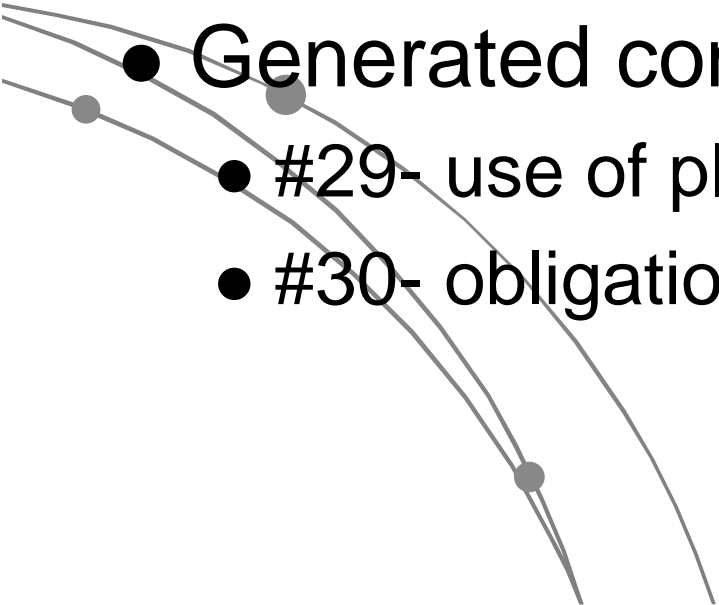
- Therapeutic versus non-therapeutic research
 - Independent review of the “Design and performance of each experimental procedure-clearly formulated in a specific protocol” (added in 1975)
- 
- A decorative graphic consisting of three curved lines that sweep from the left side of the slide towards the bottom right. Each line has a small grey circular dot placed on it. The lines are thin and grey, and the dots are also grey.

Declaration Of Helsinki

pre-2000 contributions

- Explicitly allowed permission from a legal guardian
 - Research not in accordance with Helsinki principles should not be accepted for publication.
- 
- A decorative graphic consisting of three curved lines that sweep from the left side of the slide towards the bottom right. Each line has a small grey dot at its starting point on the left.

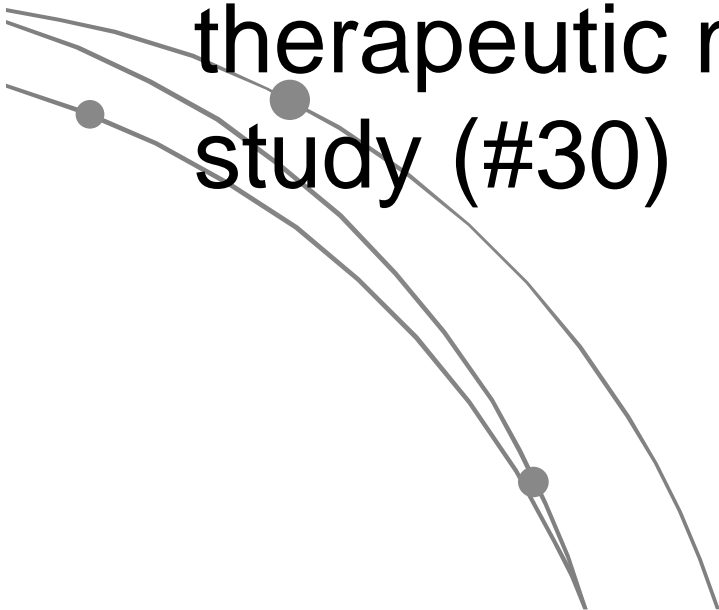
Declaration Of Helsinki 2000

- Greatly expanded
 - Change in structure
 - Generated considerable controversy, esp.
 - #29- use of placebos
 - #30- obligations for treatment post-trial
- 

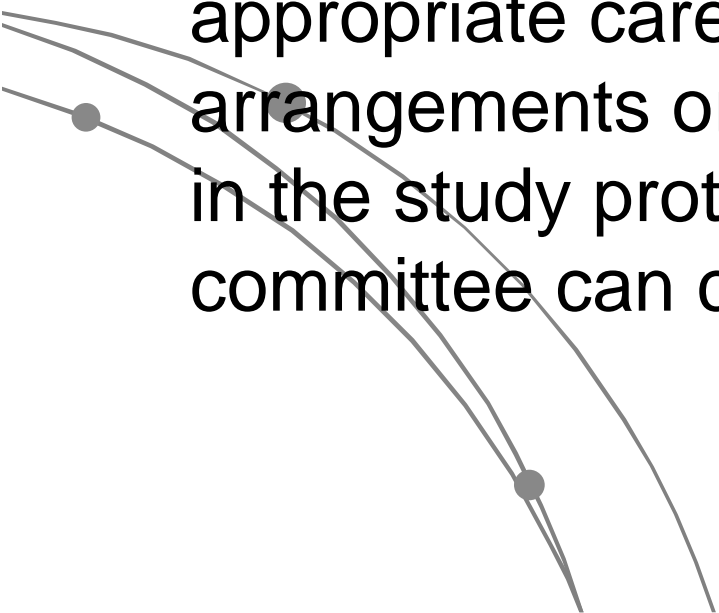
Declaration Of Helsinki

(2000)

- At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic, and therapeutic methods identified by the study (#30)

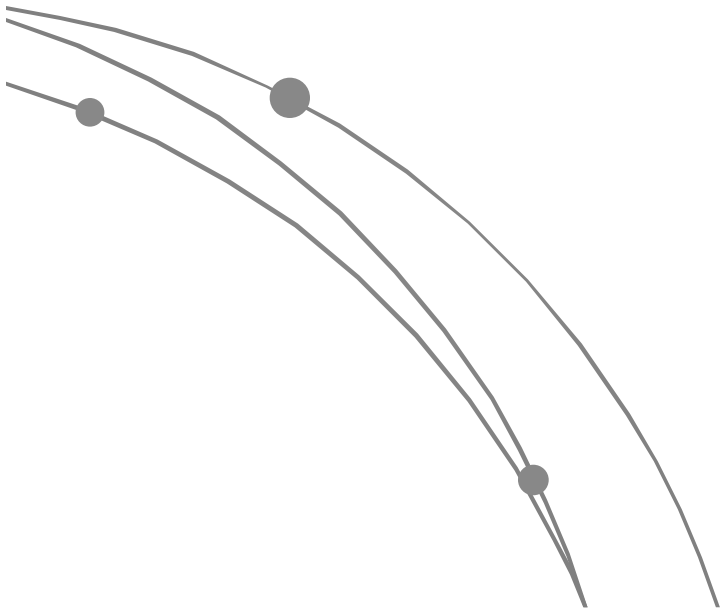


Declaration of Helsinki clarification 2004

- “The WMA reaffirms ... that it is necessary during study planning process to identify post-trial access by study participants to prophylactic, diagnostic, or therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee can consider [them]...”
- 

Current revision status

- Sixth revision was adopted by WMA in October 2008.



- “The declaration has only limited legal authority but has gained considerable moral authority. As such it is more symbolic than instrumental”




● Goodyear M et al. BMJ 29 Sept 2007

Codes of Research Ethics

- The Nuremberg Code
 - The Declaration Of Helsinki
 - The Belmont Report
 - CIOMS/WHO International Ethical Guidelines For Biomedical Research Involving Human Subjects
 - ICH/GCP-International Conference on Harmonization- Good Clinical Practice
- 

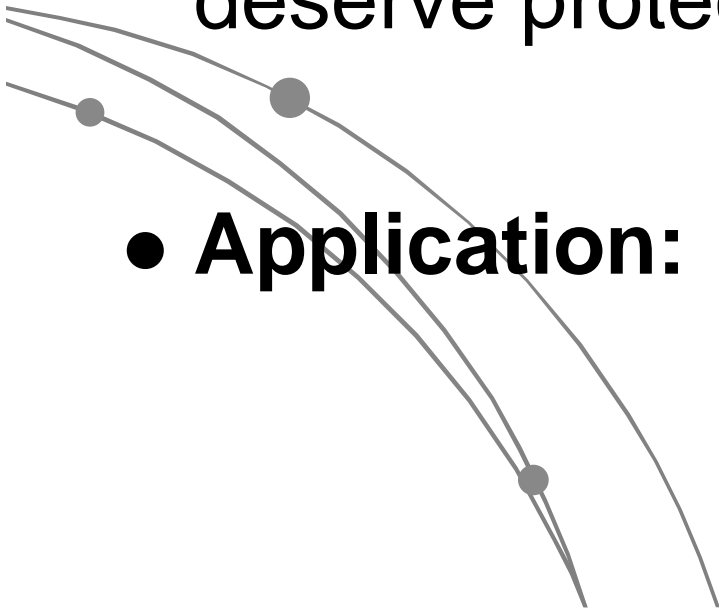
The Belmont Report

National Commission for the Protection of Human Subjects of
Biomedical and Behavioral Research 1979

- Boundaries between research and practice
 - Ethical principles underlying the conduct of research:
 - Respect for persons
 - Beneficence
 - Justice
- 
- A decorative graphic consisting of three curved lines that sweep from the left side of the slide towards the bottom right. Each line has a small grey circular dot placed on it. The lines are thin and grey, and the dots are also grey.

Respect For Persons

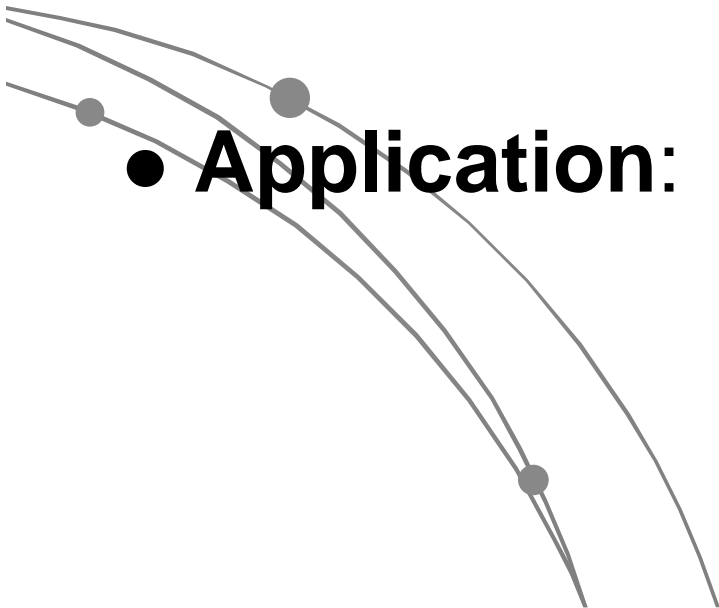
- Individuals should be treated as autonomous agents (capable of self-determination)
- Persons with diminished autonomy deserve protection
- **Application:** Informed consent



Beneficence

- Two general complementary rules:
 - Do not harm
 - Maximize possible benefits and minimize possible harms

- **Application:** Risk/Benefit assessment

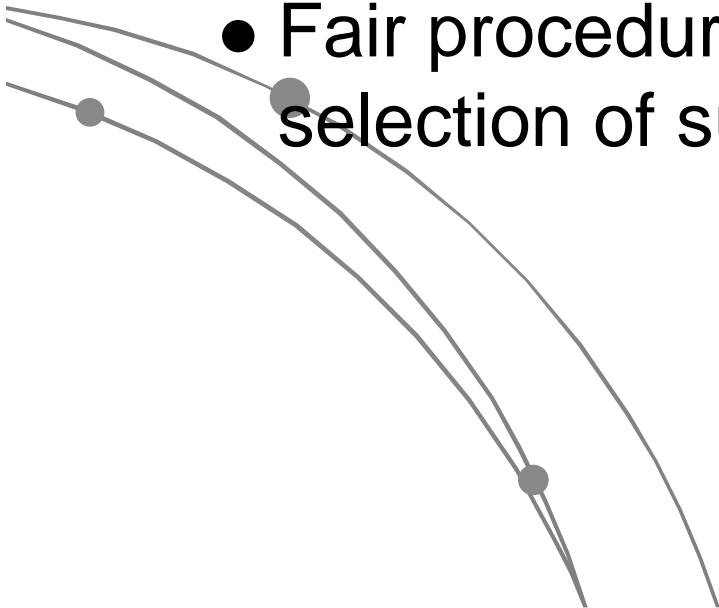


Justice

- Fairness in the distribution of the benefits and burdens of research

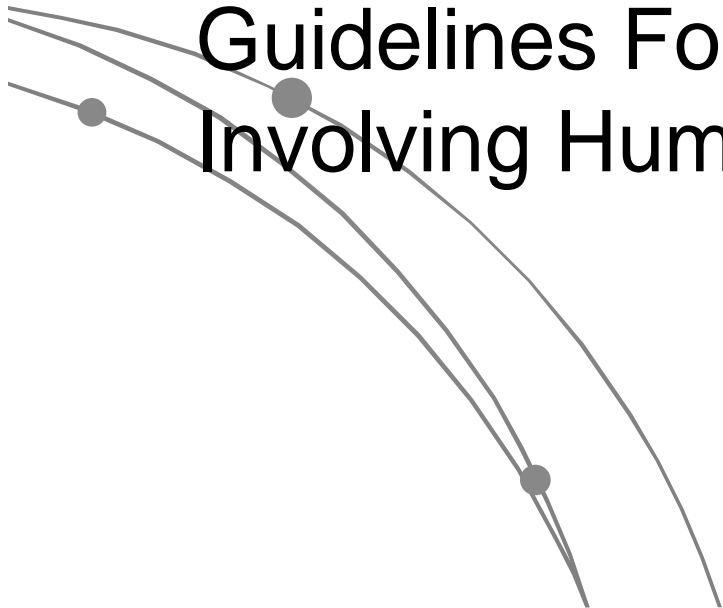
- **Application:**

- Fair procedures and outcomes in the selection of subjects



Codes of Research Ethics

- The Nuremberg Code
- The Declaration Of Helsinki
- The Belmont Report
- CIOMS/WHO International Ethical Guidelines For Biomedical Research Involving Human Subjects



International Ethical Guidelines- CIOMS

- Council for International Organizations of Medical Sciences (CIOMS)/WHO)

- Application of the Declaration of Helsinki to the particular circumstances of developing countries

- <http://www.cioms.ch/>

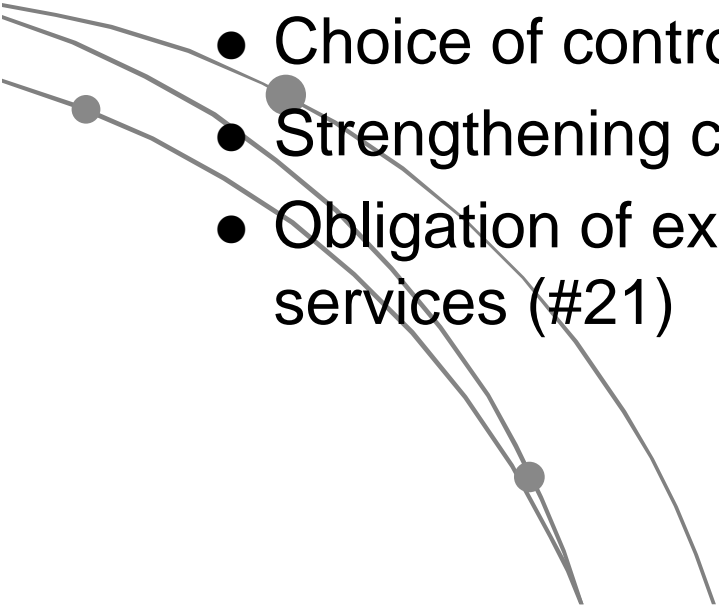
CIOMS guidelines

- International Ethical Guidelines for Epidemiological Studies 2008

http://www.cioms.ch/080221feb_2008.pdf

- 
- International Ethical Guidelines for Biomedical Research Involving Human Subjects 1993, 2002

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)

- 21 Guidelines with extensive commentary
 - 2002 additions:
 - Ethical justification and scientific validity (#1)
 - Benefits and Risks (#8)
 - Limitations on risk for those who cannot consent (#9)
 - Choice of controls (#11)
 - Strengthening capacity (#20)
 - Obligation of external sponsors for health care services (#21)
- 

CIOMS International Ethical Guidelines

- Responsiveness to the health needs and priorities of the community
- ‘Reasonable availability’
- Rights of subjects to compensation for research injury

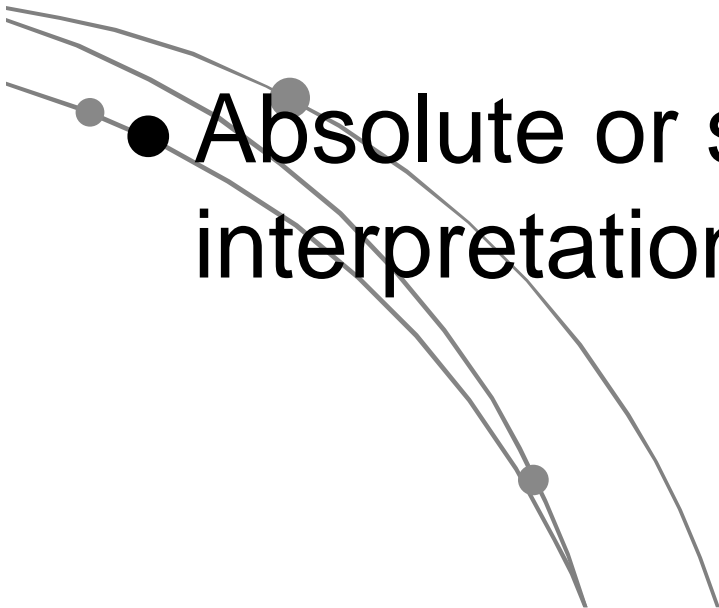


How are codes and guidelines to be used?

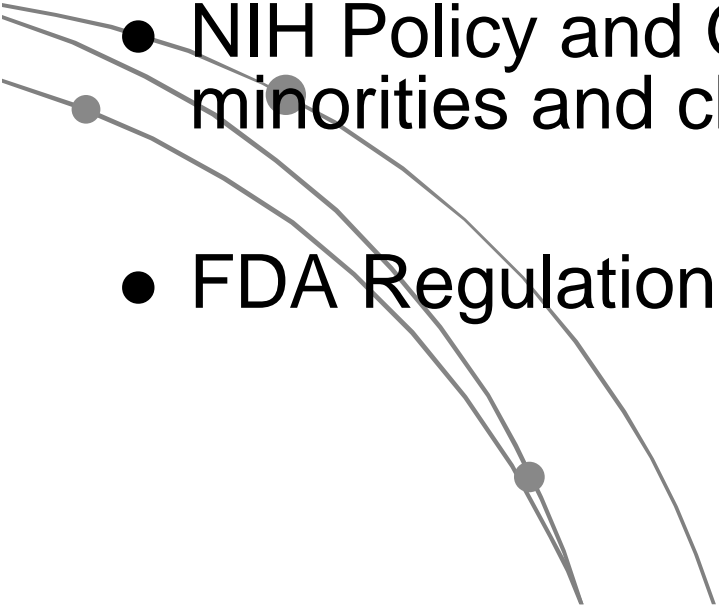
- Authority?

- Universal?

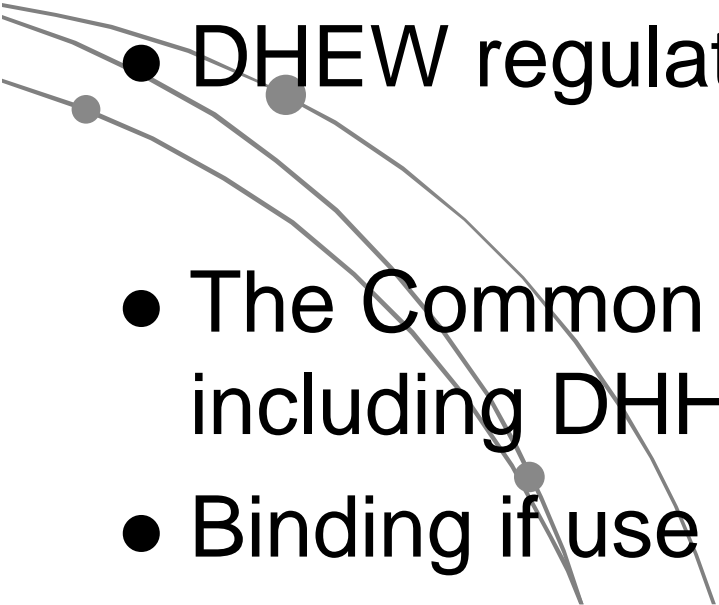
- Absolute or subject to revision and interpretation?



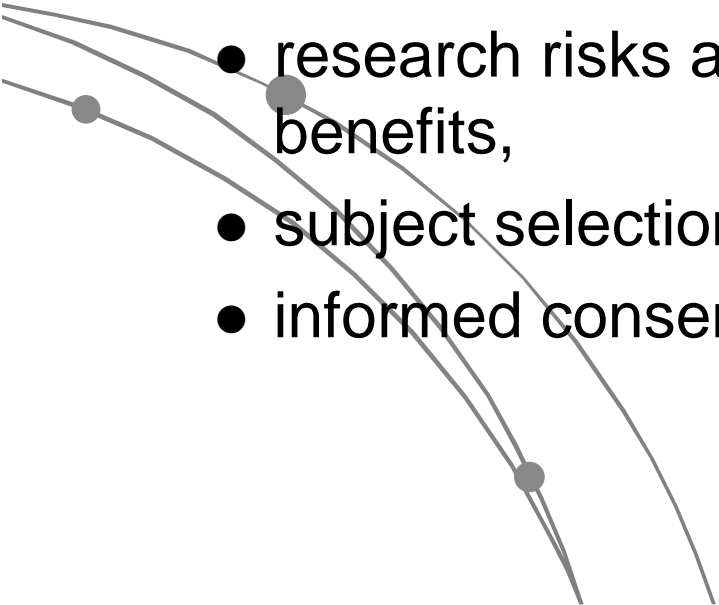
U.S. Federal Regulations and Guidelines

- Title 45 US CFR 46
 - The Common Rule
 - Additional subparts
 - Federal Wide Assurance
 - NIH Policy and Guidelines on women, ethnic minorities and children
 - FDA Regulations (21 US CFR 50 AND 56)
- 
- A decorative graphic consisting of three curved lines that sweep from the left side of the slide towards the bottom right. Each line has a small grey dot placed on it. The lines are thin and grey, and the dots are also small and grey.

45 CFR 46 Protection of Human Subjects

- PHS policy 1966
 - National Research Act (1974)
 - DHEW regulations (1981)
 - The Common rule- 17 Federal agencies, including DHHS (1991)
 - Binding if use HHS funds or support
- 

45 CFR 46 Protection of Human Subjects (Subpart A, Common Rule)

- Composition and function of a local institutional review board (IRB)
 - Requirements for informed consent
 - IRB to assure that:
 - risks are minimized,
 - research risks are reasonable in relation to expected benefits,
 - subject selection is equitable, and
 - informed consent will be obtained from each subject.
- 

45 CFR 46 Protection of Human Subjects

- Subpart B- Fetuses, pregnant women, and human *in vitro* fertilization
- Subpart C- Prisoners as subjects
- Subpart D- Children
- Subpart E- IRB Registration
- ?future subparts?

Assurance of Compliance with Federal Regulations

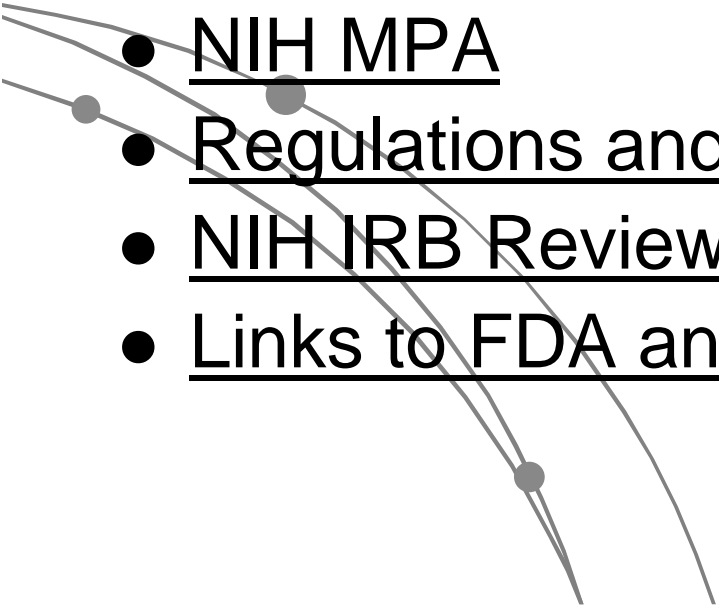
- Office of Human Research Protections (OHRP)

<http://www.hhs.gov/ohrp>

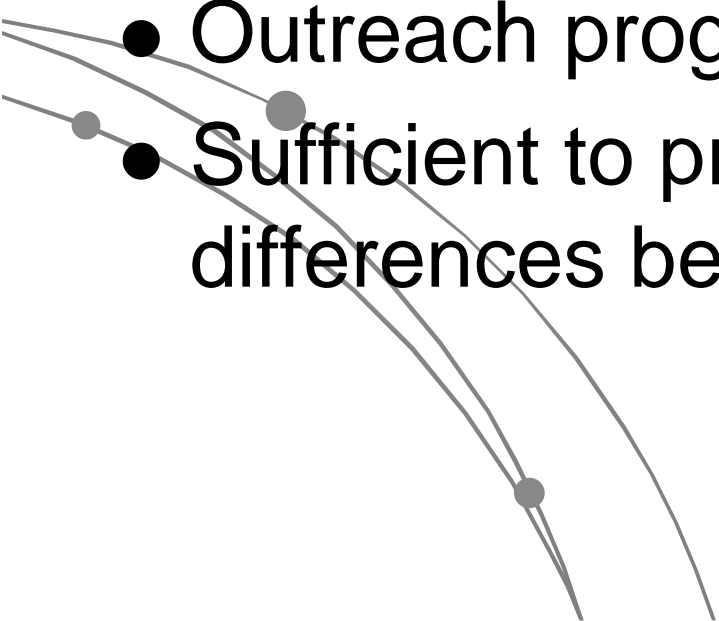
- Federal Wide Assurance (FWA)

- Intramural Office of Human Subjects Research <http://ohsr.od.nih.gov/>

OHSR/ NIH

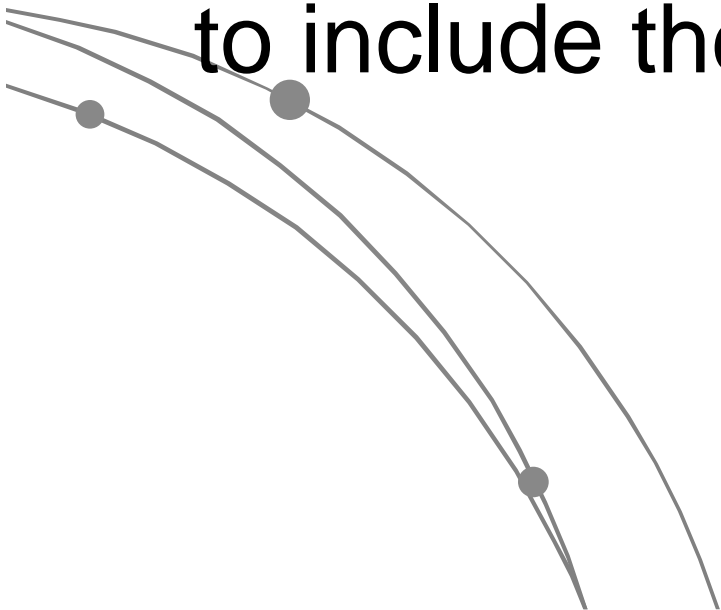
- About the OHSR
 - OHSR Information Sheets and Forms
 - Computer-Based Training
 - Adverse Event Reports
 - Human Subjects Research Advisory Committee
 - NIH MPA
 - Regulations and Ethical Guidelines
 - NIH IRB Review Process
 - Links to FDA and Other Sites
- 

NIH guidelines on the inclusion of women and minorities

- NIH Reauthorization Act (1993).
 - Women and members of ethnic minority groups are to be included (some exceptions)
 - Outreach programs for recruitment
 - Sufficient to provide for a valid analysis of differences between groups
- 

NIH Policy and Guidelines on the Inclusion of Children as Participants in Research

“...children must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them...” (Effective October 1, 1998)



FDA REGULATIONS

- 21 CFR 50 Protection of Human Subjects (informed consent)
 - Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products (21 CFR Part 50, subpart D)
- 21 CFR 56 Institutional Review Boards
 - Some differences from the common rule.
 - Binding if performing clinical investigation of FDA-regulated product (thus can be under *both* OHRP and FDA Regs)

FDA Regulations Relating to Good Clinical Practice and Clinical Trials

<http://www.fda.gov/oc/gcp/regulations.html>

- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Investigational New Drug Application (21 CFR Part 312)
- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
- Applications for FDA Approval of a Biologic License (21 CFR Part 601)
- Investigational Device Exemptions (21 CFR Part 812)
- Premarket Approval of Medical Devices (21 CFR Part 814)

FDA

- Forms 1571 (Investigational New Drug Application) and 1572 (Statement of Investigator)

- <http://www.fda.gov/cder/about/smallbiz/Forms.htm>

- FDA Information Sheet Guidances for Institutional Review Boards, Clinical Investigators, and Sponsors

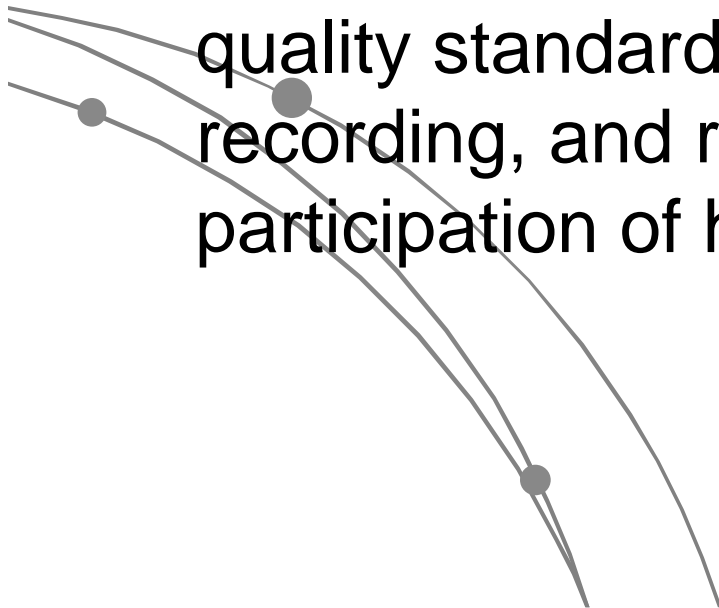
- <http://www.fda.gov/oc/ohrt/irbs/default.htm>

ICH

- “The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)... brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.”
 - <http://www.ich.org/cache/compo/276-254-1.html>
- 

ICH Harmonised Tripartite Guideline-GCP (E6-(R1) 1996)

- Objective: “...to provide a unified standardfor mutual acceptance of clinical data by regulatory authorities in those jurisdictions”
- GCP-”...an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects”

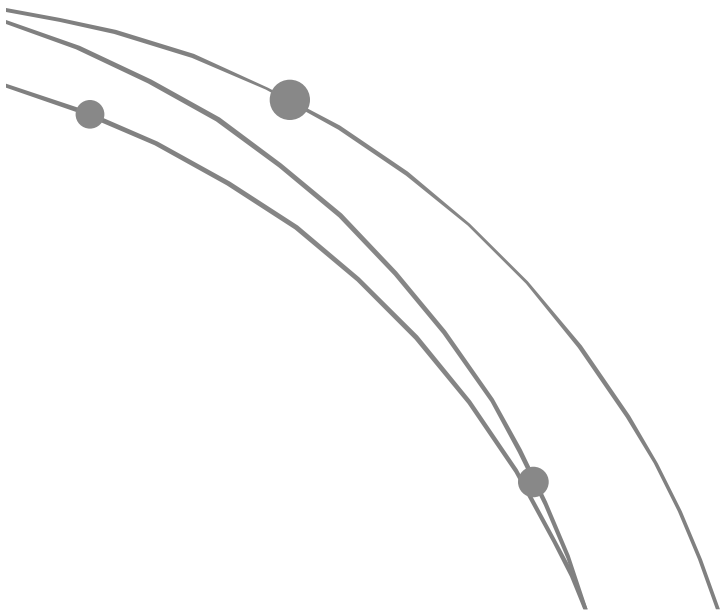


ICH-Guideline for Good Clinical Practice

- “Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical data are credible” (ICH-E6)
- Adopted by US FDA as Good Clinical Practice: Consolidated Guideline (1997); for foreign studies, can use in lieu of DoH:
<http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480537f08>
- <http://www.ich.org>

So, which rules and guidance
should I follow?

- For *HHS funded* research:
45 CFR 46, Subparts A through D



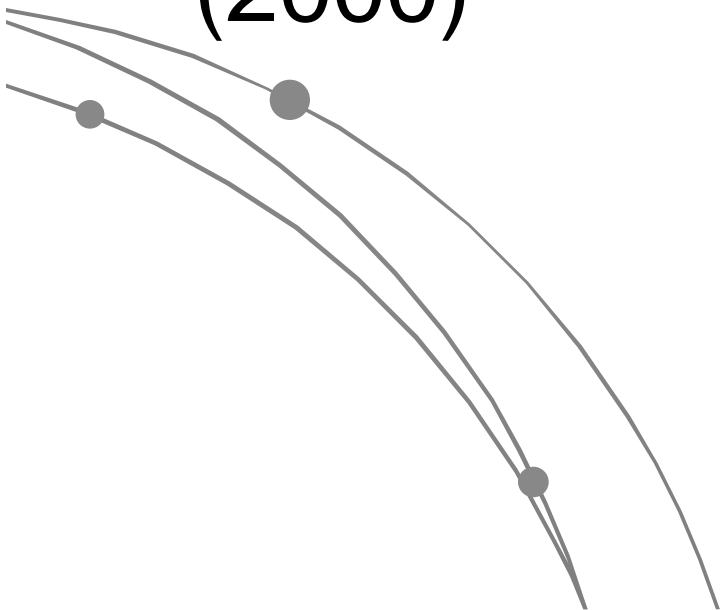
So, which rules and guidance should I follow?

- For research testing a *drug, biologic, or device* under an IND (or equivalent) or that may ultimately be submitted for FDA approval- 21 CFR 50 and 56 and ICH/GCP

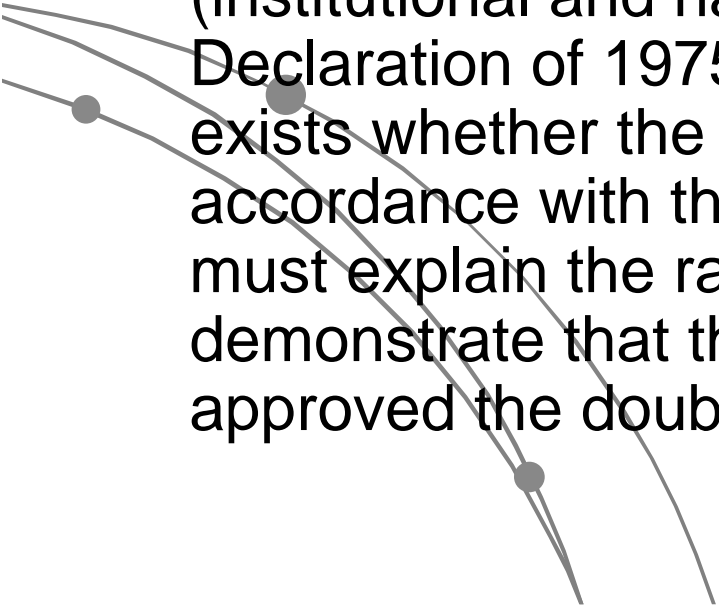
- If above trials are *funded by NIH*- also 45 CFR 46

So, which rules and guidance should I follow?

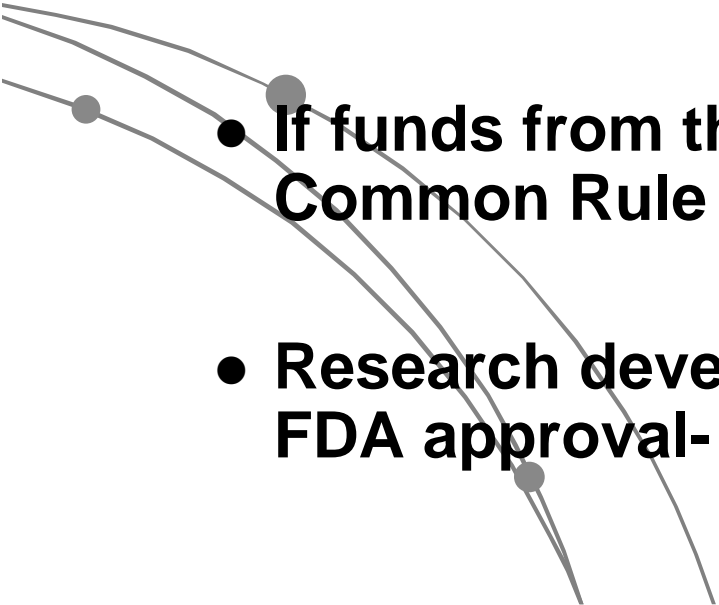
- If you want to publish your research in a major medical journal – note issue relating to Declaration of Helsinki (2000)



So, which rules and guidance should I follow?

- International Committee of Medical Journal Editors, www.icmje.org
 - [A]uthors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.
- 

So, which rules and guidance should I follow?

- For international research:
 - **The legal and ethical requirements of the host jurisdiction**
 - CIOMS guidelines and Helsinki
 - **If funds from the US government-- generally Common Rule and perhaps subparts**
 - **Research developing a product that may need FDA approval- ICH/CGP**
- 

Which codes?

- An NIH-funded investigator is conducting a randomized, placebo controlled study of a new drug for arthritis. She intends to publish the results.

- 
- Which codes should she follow?