U.S. FOOD & DRUG ADMINISTRATION

FDA Genetic Toxicology Workshop

FDA Requirements for the Protection of Healthy Subjects in Phase 1 Clinical Trials

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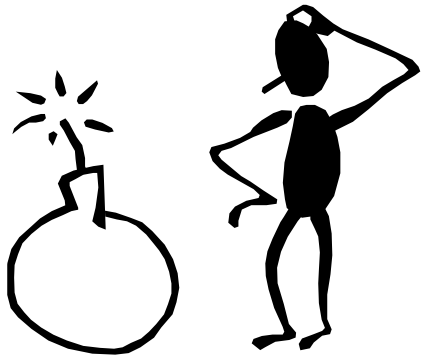
Disclosure

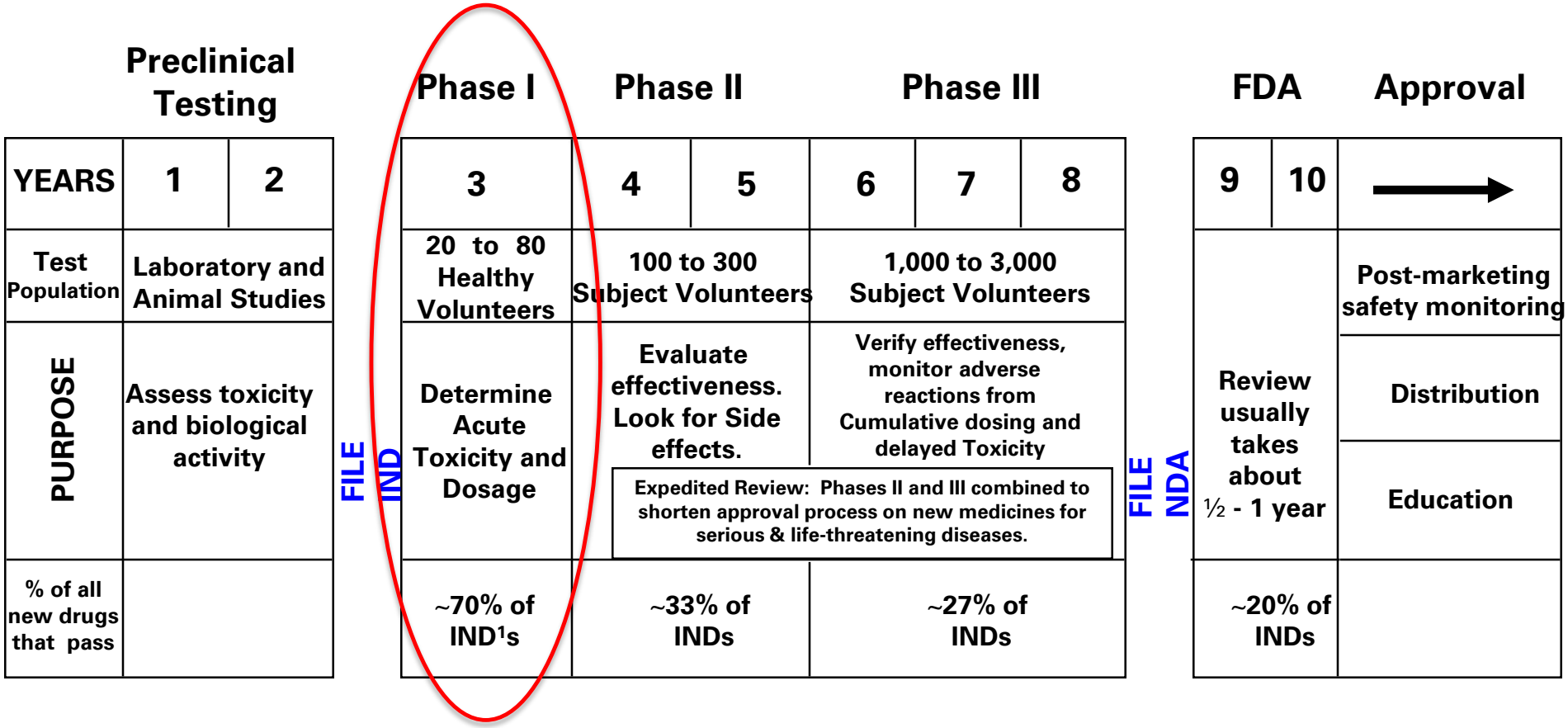
- The views expressed in this presentation are my own and do not necessarily represent the policy of either the U.S. Food and Drug Administration (FDA) or the U.S. Department of Health and Human Services (HHS).



Objectives

- Provide a general overview of FDA requirements for the protection of (healthy) subjects
- Provide a general overview of what ethical principles are considered when evaluating a Phase 1 clinical trials offering no prospect of direct benefit to healthy subjects

Classic Drug Development and Review Process



1. IND (Investigational New Drug Application)

The Key Concerns

- Phase 1 clinical trials typically do not offer the prospect of direct benefit to healthy subjects
- Healthy subjects not likely to benefit from the product development program because they do not have the targeted condition
- Preclinical work may be suggestive of a safety signal or incomplete
- Need to assure healthy subjects are not unduly influenced into participating in the research
- Consent document (and process) needs to be clear and balanced to minimize misunderstandings and limit undue influence

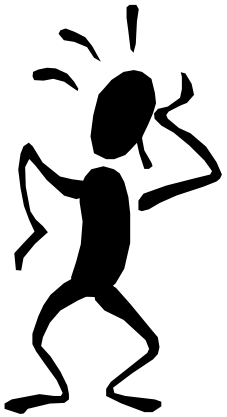
Investigational New Drug Application Contents

(abbreviated list, see 21 CFR 312.23)

- Several commitments including Informed Consent and Institutional Review Board (IRB) oversight
- Summary of past human experience (to include risk)
- Description of the overall plan for investigating the product to include rationale for use, indication to be evaluated, etc.
- Summary of pharmacokinetic (PK) and absorption/distribution/metabolism/excretion (ADME) studies
- Protocol for planned study(ies)
- Chemistry, manufacturing, and control information
- Description of drug substance
- Pharmacology and toxicology information
- "Relevant information" as needed (e.g., consent document)

Crosses multiple disciplines to include Ethics

Regulations for the Protection of Human Subjects



- 21 CFR Part 50: “Protection of Human Subjects”
  - Primarily relates to informed consent and additional safeguards for research involving children
- 21 CFR Part 56: “Institutional Review Boards” (IRB)
  - Primarily relates to IRB operations
- Human Subjects Protections are also built into many of the requirements under 21 CFR 312 and other FDA regulations

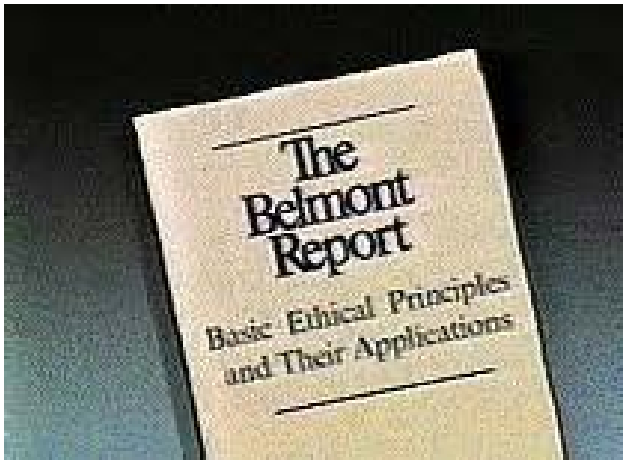
There are no specific or unique Human subject protections regulations that apply to research involving healthy subjects. The issue is how do we apply the existing regulations to this population.

Primary Framework for U.S. Regulations

Regulations based on Good Clinical Practice (GCP) standards and embody the Belmont principles

Belmont Principles

1. Respect for persons
2. Beneficence
3. Justice



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

April 18, 1979

Ethical Framework for Regulations

- **Respect for persons**
  - Informed consent, consent of legally authorized representative, assent
  - Additional protections for vulnerable subjects
  - Privacy/confidentiality
- **Beneficence**
  - Risks to subjects are reasonable in relation to anticipated benefits
  - The risk to benefit assessment is at least as favorable as available alternative approaches
  - Qualification of Investigator
  - Trial design
- **Justice**
  - Selection of subjects is equitable
  - Inclusion/exclusion criteria
  - Recruitment

IRB Criteria for Approval of Research

21 CFR 56.111(a)

- Risk to subjects are minimized
- Risk to subjects are reasonable in relation to anticipated benefit, if any, to subjects and the importance of the knowledge that may be expected to result
- Selection of subjects is equitable
- Informed consent will be obtained and documented
- Where appropriate, plans for monitoring the data collect to ensure subject safety
- Adequate provisions to protect privacy and confidentiality

21 CFR 56.111(a)(2)

- "Risks to subjects are reasonable in relation to anticipated benefit, if any, to subjects, and the importance of the knowledge that may be expected to result."
  - Payment to subjects and the healthcare provided during the research are not considered "benefits" for the purpose of justifying risk.
  - Risk should be considered in the context of the Social Value the research offers

Social Value

- Social value can be thought of as a goal to have a research hypothesis that asks an important public health question
  - For Phase 1 trials the expectation would be that the study contributes in a significant way to the development plan of the investigational product
  - There are limits as to how much risk can be justified in healthy volunteers by Social Value alone
    - Many ethicists believe potential harms should not be irreversible, lead to permanent disability, or be potentially fatal; others believe there is a need to balance paternalism with autonomy[1]
    - It is helpful to quantify risk whenever possible; however, the decision of acceptable risk is a judgment call

1 Resnik D.B., "Limits on risks for healthy volunteers in biomedical research", Theor. Med. Bioeth (2012) 33:137-149

Paternalism vs Autonomy

- Nuremberg Code (1947):
  - "No experiment should be conduced where there is an a priori reason to believe that death or disabling injury will occur: except perhaps, in those experiments where the experimental physician also serve as subjects"
- Declaration of Helsinki (1964)
  - "Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject."
- Council for the International Organization of Medical Sciences, International Ethical Guidelines for Health-Related Research Involving Humans (2016)
  - "…researchers, sponsors, and research ethic committees must ensure that the risk are reasonable In light of the social and scientific value of the research, and that the study does not exceed an upper limit of risk to study participants."

General Requirements for Informed Consent

21 CFR 50.20

- *"…An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."*
  - FDA does not consider payment to subjects a benefit that can be used to justify risk.
  - Payment to subjects can contribute to undue influence
    - e.g., Withholding entire payment contingent upon completion of the study
  - Reimbursement for research related expenses (e.g., travel, lodging food etc.) are not considered to create undue influence
  - Consent document should clarify all payments
  - The time allotted for obtaining consent and the circumstances in which it is obtained is important to consider
  - Right to withdraw at anytime must be respected
  - Consider compensation for injury

Informed Consent: 21 CFR 50.25

Required Basic Elements

1. Study involves research
   - Purpose
   - Expected duration
   - Description of procedures/experimental components
2. Reasonably foreseen risks or discomforts
3. Reasonably foreseen benefits to the subject or to others
4. Appropriate alternatives
5. Confidentiality/FDA may inspect
6. Compensation in general and for research-related injury
7. Point of contact for questions
8. Participation is voluntary

Additional Elements (When Appropriate)

- The particular procedure may involve unforeseeable risk to the subject (embryo or fetus)
- Circumstances of termination
- Costs to the subject
- Consequences of withdrawal
- Significant new findings may be communicated
- Approximate number of subjects

Applicable Clinical Trials

- Mandatory verbatim statement related to posting on ClinicalTrials.gov

Consent Document and Process

- Discussion about risks should be clear
  - Significant risks should be emphasized
  - Consider tests to assess understanding if risks are substantially high and/or difficult to understand
- Statement about lack of benefit must be clear
  - Do not conflate with payments and or healthcare services provided during the trial
  - Social value can be described but should be balanced (i.e., avoid overly optimistic or misleading statements)
- Amounts and process for paying subjects should be described
  - Avoid creating undue influence (e.g., withholding the entire payment until the end for a multi-visit type study)

Grounds for Clinical Hold (21 CFR 312.42(b)(1))

Phase 1

- Unreasonable and significant risk
- Unqualified clinical investigator
- Investigator brochure is misleading, erroneous, or materially incomplete
- IND does not contain the information required under 312.23
- Gender exclusion for investigational products with reproductive-toxicology concerns

What do I look for in my review

1. Are the risks reasonable, minimized, and justified by the potential social value of the trial?
2. Is there a robust informed consent document and process?
3. Are vulnerable populations protected?
4. Is the right to withdraw respected?
5. Is the level of compensation adequate but not undue?
6. Have independent expert reviews been conducted?
7. Is there a system of compensation for injury?
8. Is there adequate safety monitoring (short/long term)?
9. Are there alternative approaches/populations that would be more justifiable?

Thank You

Questions for me?

Resources

- 21 CFR Part 50 Protection of Human Subjects
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50
- 21 CFR Part 56 Institutional Review Boards (IRB)
  - https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56
- FDA Guidance Document Search Tool
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents#guidancesearch
- FDA Guidance "Payment and Reimbursement to Research Subjects"
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects
- FDA Guidance "Informed Consent"
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/informed-consent
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