Protection of Human Participants in Research

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Human Subjects in Research

Why do people choose to participate as research subjects?

Human Subjects in Research

What are the responsibilities of the researchers towards the human subjects who choose to participate?

Credo of Clinical Research

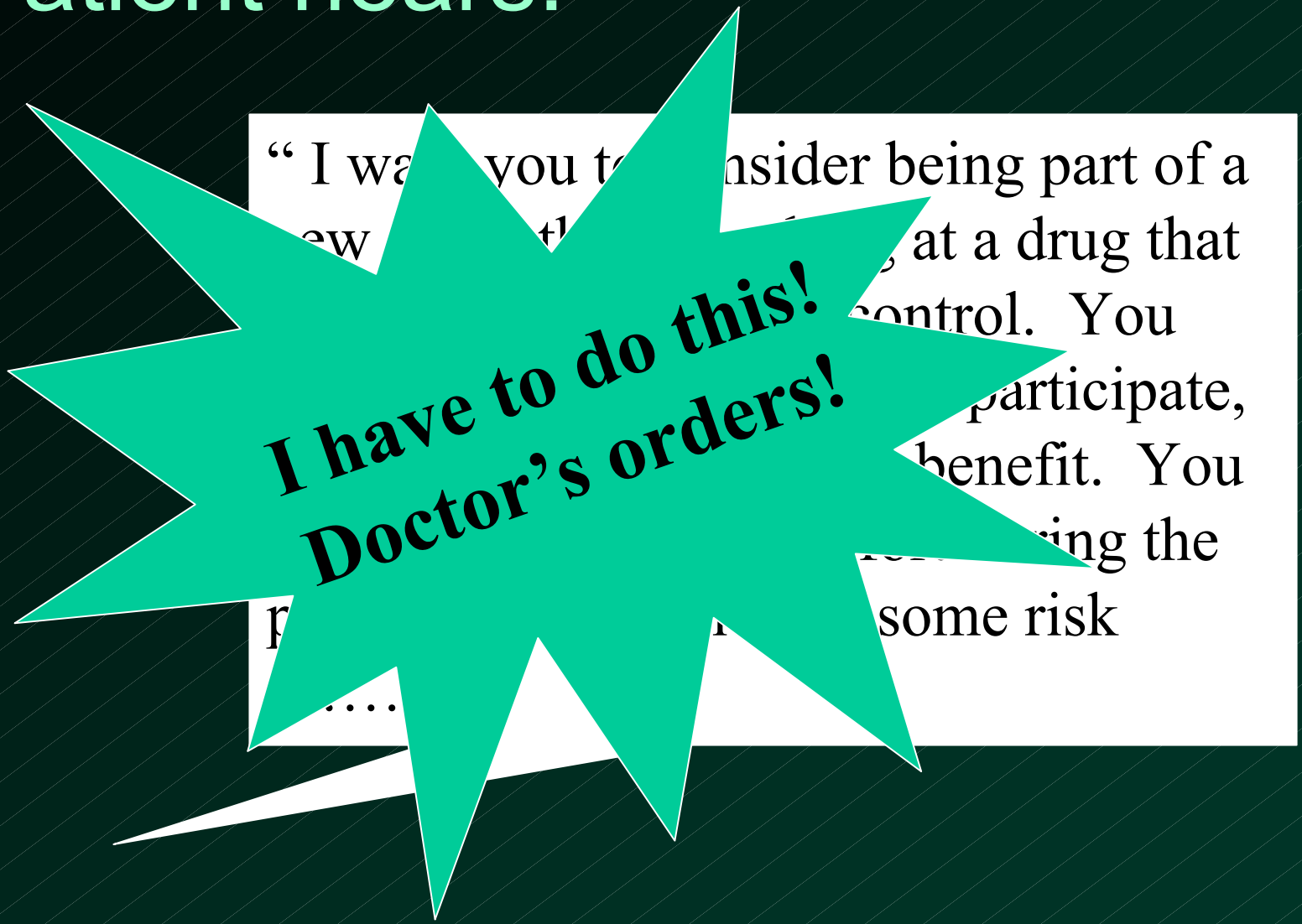
Research is a
Privilege, not a Right

...especially when Human Subjects are involved

Physician says:

" I want you to consider being part of a new study that is looking at a drug that may help with bladder control. You should not feel obligated to participate, and I can't guarantee any benefit. You may experience discomfort during the procedures, and there is some risk of……

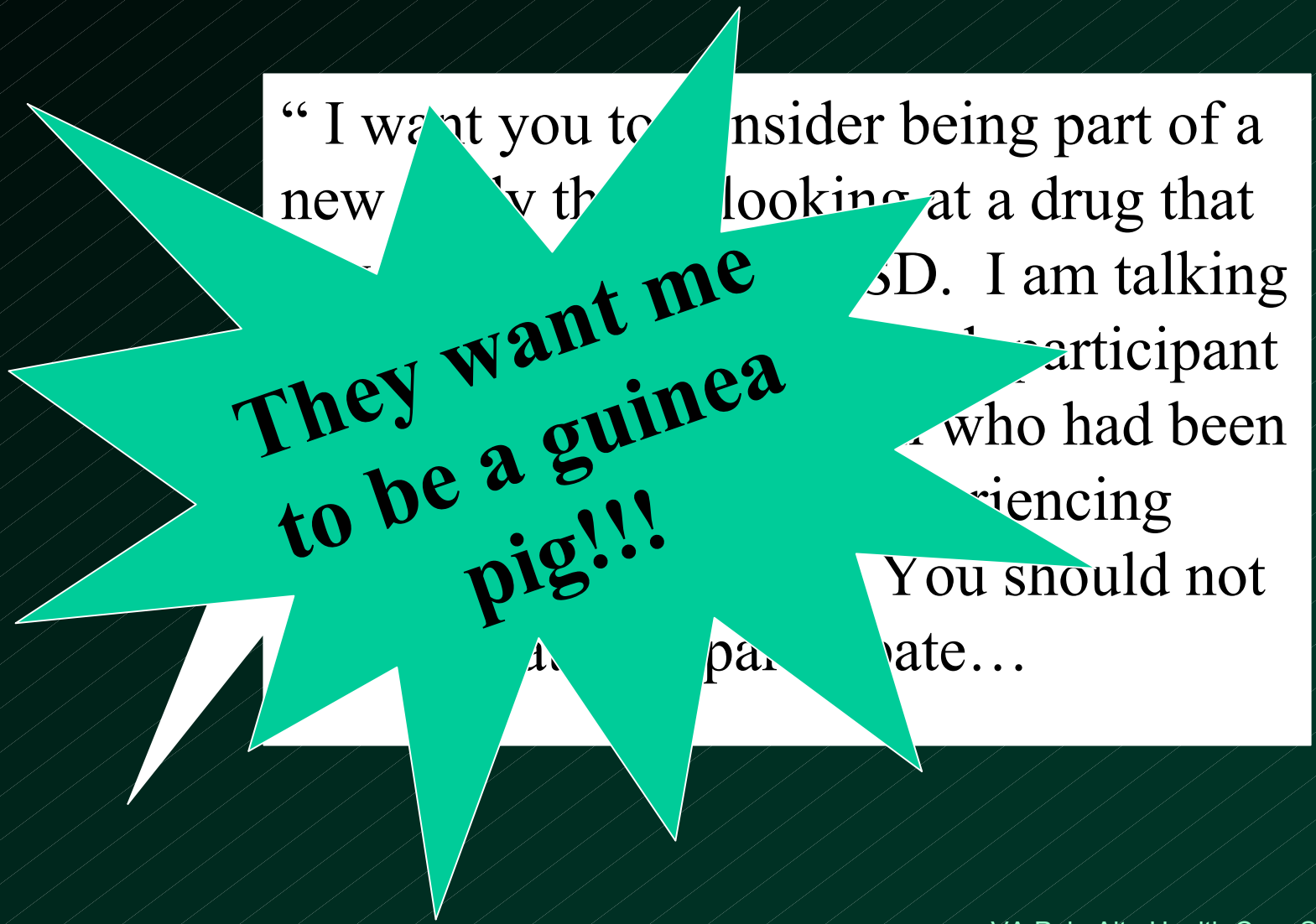
Patient hears:



Study Coordinator says:

" I want you to consider being part of a new study that is looking at a drug that may help with your PTSD. I am talking to you as a possible research participant because you are a veteran who had been in combat and may be experiencing some effects of PTSD. You should not feel obligated to participate…

Patient hears:



Neurosurgeon Researcher says:

" I want to invite you into a research study that is looking at how your body responds after a spinal cord injury. We will be making measurements of your brain to see what happens when you try to move your arm or hand. There is no treatment as part of this study, but we may learn important information that can help us in the future…

Patient may hear:

Overview of Talk

- Principles and Regulations Governing Human Research
- Process of Institutional Review for the Protection of Human Subjects
- Responsibilities of Clinical Researcher

Brief History of Codes & Regulations for Protection of Human Subjects

4th Century AD - Ancient Standard of Medicine

- Hippocrates exhorts physicians: “Do no harm” and “Maintain as confidential that which is told to them”

1947 - Nuremburg Code

- Written by American judges in response to Nazi atrocities
- 1st principle: “Informed consent of the subject is absolutely essential”

1966 - Assurance of Institutional Review

- Memo from Surgeon General requiring institutions in receipt of federal funding to review of research activity for protection of human subjects
- Establishment of Institutional Review Boards (IRB)

Brief History of Codes & Regulations for Protection of Human Subjects

1974 - Title 45 Code of Federal Regulations Part 46

- First federal regulations, formalized the system already present
- Institutional assurances, institutional committees, diversity in membership, open-ended and subjective review process

1979 - The Belmont Report

- Result of nearly four years of discussion, formulated by the National Commission on the Protection of Human Subjects in Biomedical and Behavioral Research (appointed July 1974)
- Cornerstone statement of ethical principles for human subjects
- Basis of current system of IRB review and informed consent

Brief History of Codes & Regulations for Protection of Human Subjects

1981 - Title 21 CFR Parts 50 and 56

- FDA regulations regarding drugs, devices, and biologics
- Similar, but not identical to 45 CFR 46

1991 - The Common Rule

- Various rules and regulations of 17 federal agencies reconciled and consolidated into one document
- Integrated into 45 CFR 46
- Concepts currently adopted by private foundations & institutions as well as federal agencies

The Belmont Report (1979)

The Commission was directed to consider:

i) Boundaries between biomedical and behavioral research and the accepted and routine practice of medicine,

ii) The role of assessment of risk-benefit criteria in the determination of the appropriateness of research involving human subjects,

iii) Appropriate guidelines for the selection of human subjects for participation in such research, and

iv) The nature and definition of informed consent in various research settings.

The Belmont Report

Boundaries between Practice and Research

- "Practice" commonly refers to interventions designed solely to enhance the well-being of an individual patient with a reasonable expectation of success
- "Research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge
- *Practice* and *Research* can be carried on together; if so, regulations for protection of human subjects apply

The Belmont Report - 1979

Established Ethical Principles and Guidelines for the Protection of Human Subjects of Research

Basic Principles:

1) Respect for Persons
2) Beneficence
3) Justice

Principle 1: Respect for Persons

Moral requirements:

- Individuals should be treated as autonomous
- Protection of those with diminished autonomy

Application: Informed Consent

- Information
- Comprehension
- Voluntariness

Principle 2: Beneficence

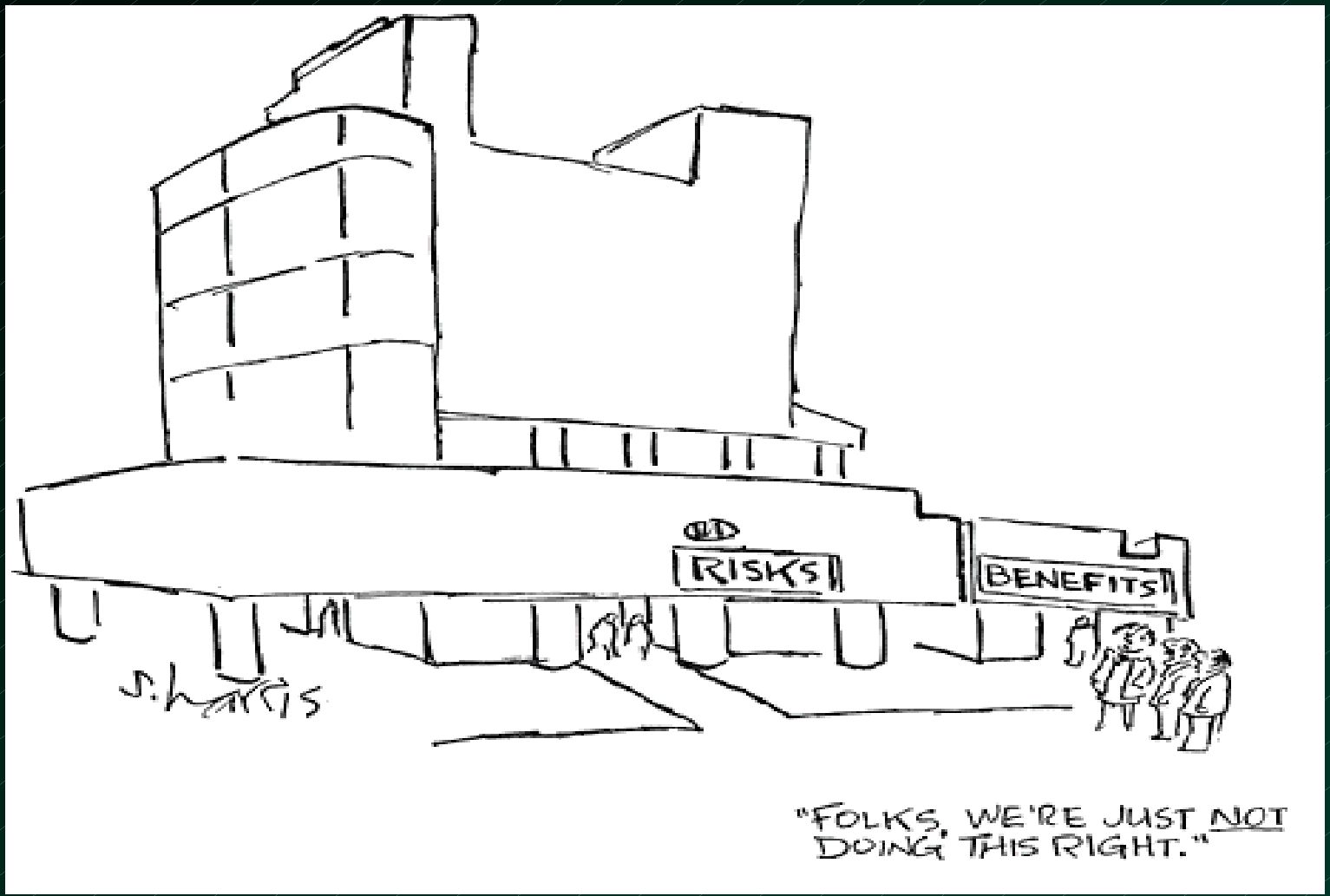
General Rules:

- "Do no harm" - fundamental principle
- Maximize possible benefits and minimize possible harms
- However, avoiding harm requires learning what is harmful

Application: Risk/Benefit Assessment

- Nature and scope of risks and potential benefits
- Systematic assessment of risks and potential benefits

“Folks, we’re just not doing this right.”



Risks versus Benefits

"Risk" refers to possibility that harm may occur.

- Often used for *both* chance of *experiencing* harm and *severity* of potential harm
- Can include physical, psychological, legal, social, and economic harm

"Benefit" refers to something of positive value related to health or welfare

- Usually not expressed as probability

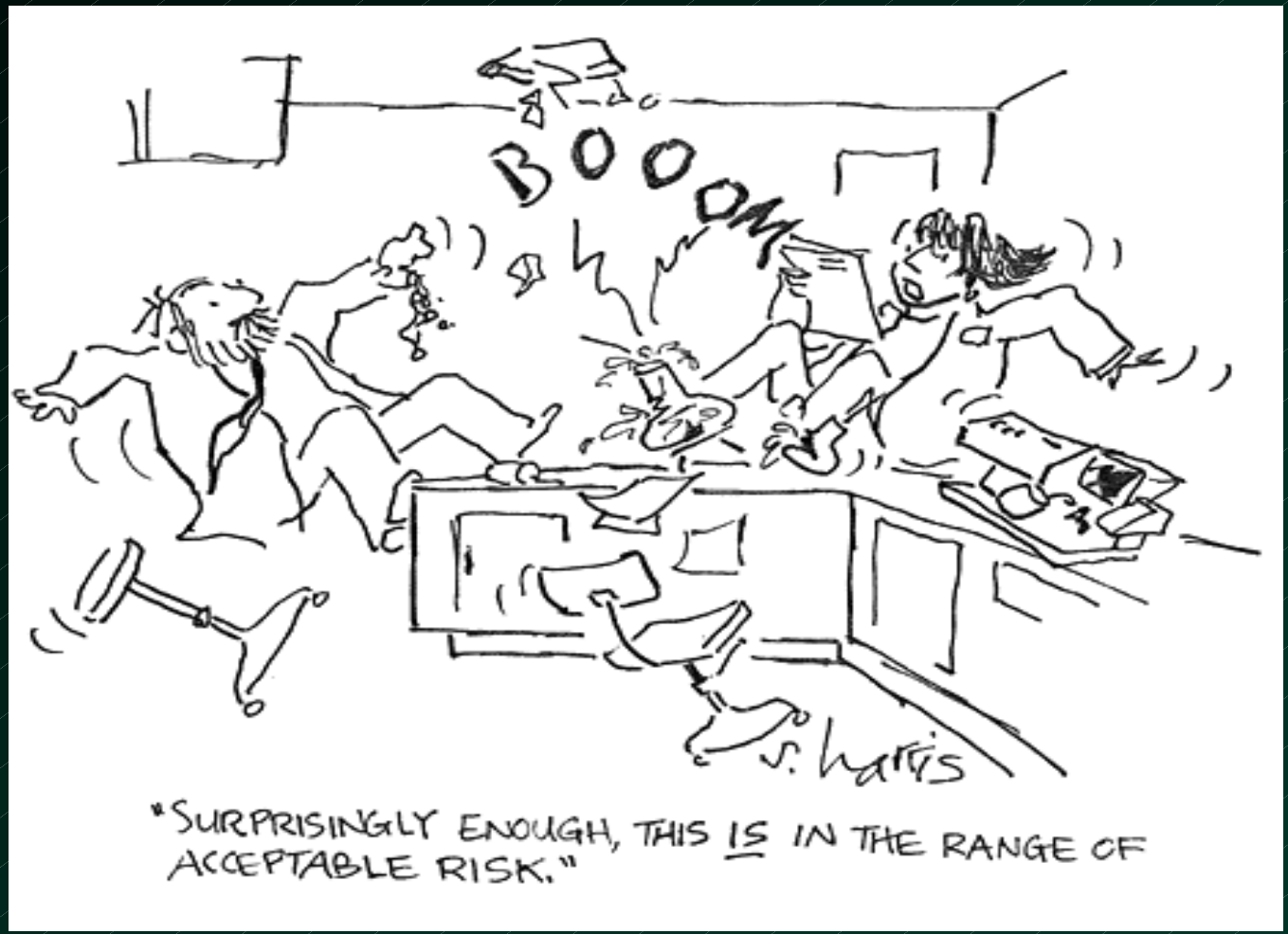
Risk to individual weighed against benefit to *individual* as well as benefit to *society* (generalizable knowledge).

Risks versus Benefits

Justification of Research should reflect:

- Reduction in risks to those necessary to achieve objective of study
- Where significant risk is involved, likelihood of potential benefit must also be high and presumably better than available alternative treatment
- Condition of particular population involved

“Surprisingly enough, this is in the range of acceptable risk.”



Principle 3: Justice

General Rules:

- Fairness in the distribution of burdens & benefits

Application: Selection of Subjects

- Investigators should not offer potentially beneficial research only to some patients who are in their favor nor select “undesirable” patients for risky research
- *Social injustice* can result from involvement of vulnerable subjects, especially those who are very sick, dependent, or economically disadvantaged and thus may be easy to manipulate because of illness or socioeconomic condition

Protection of Vulnerable Populations

Defined in 45 CFR 46 as: children, prisoners, pregnant women, *handicapped*, mentally disabled persons, economically or educationally disadvantaged persons

Additional protections afforded, especially where –

- competency to provide consent may be compromised
- or potential for coercion is excessive.

- may include exclusion from participation, in order to best protect their interests and well-being

IRB Review Process

- According to 45 CFR 46 and local/institutional rules
- Diverse membership includes researchers, laypersons, members of vulnerable groups, legal representative
- Review of research protocol, research grant (where applicable), consent forms, and all relevant documents
- Justification of use of human subjects - relative to level of risks and alternative procedures available
- Reporting of adverse events (AE)
- Periodic review of research project and progress

IRB Approval Criteria

- Risks to all human subjects are *minimized*
- Risks to human 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
- Selection of subjects is *equitable*
- Informed consent is sought from each prospective subject or legal representative
- Informed consent is documented appropriately

IRB Approval Criteria (cont.)

- When appropriate, research plan makes adequate provision for *monitoring of data to ensure safety* of human subjects
- When appropriate, there are adequate provisions to *protect privacy and maintain confidentiality*
- When some or all subjects are likely to be *vulnerable to coercion or undue influence*, additional safeguards are included to protect rights and welfare of these subjects

“I can’t make a statement to the press. That would violate the confidential relationship between the researchers and his guinea pig.”

Informed Consent

- What is this?
- How is it accomplished?
- Does it need to be documented?
- *How do you know that information that has been conveyed has been understood?*

Informed Consent

Required Elements - per The Common Rule

1) A statement that the study involves research
   - *Explanation of the purpose of the research*
   - *Expected duration of participation*
   - *Detailed description of procedures*
2) Description of reasonably foreseeable risks or discomforts
   - *Risks should be mentioned according to their severity and/or probability*

Informed Consent

Required Elements (continued)

3) Description of any benefits to the subject or others which might reasonably be expected

- *Researchers should present a realistic evaluation of benefits*
- *If anything, present bias against possible benefits; patients often interpret "new" or "experimental" as "better"*
- *Outcome of trial must not be presumed*

Informed Consent

Required Elements (continued)

4) Disclosure of alternative procedures or courses of treatment
   - *A decision made without options is no decision*
5) Statement regarding confidentiality of records
6) For research involving more than minimal risk, explanation regarding compensation, treatment to be provided if injury occurs, and institutional liabilities and how to obtain treatment and/or compensation

Informed Consent

Required Elements (continued)

7) Explanation of whom to contact for information about research and research subjects' rights and whom to contact for research-related injury

8) Statement that:

   participation is voluntary,

   refusal to participate will involve no penalty or loss of benefits to which subject is otherwise entitled, and

   subject may discontinue participation at any time without penalty or loss of benefits (as above)

Informed Consent

Additional Elements - as appropriate

1) Statement that treatment or procedure may impose risks to subject that are currently unforeseeable
2) Anticipated circumstances for termination of subjects' participation by investigator
   - *Includes non-compliance, consideration of subjects' best interests, unanticipated circumstances, etc*
3) Additional costs to subject resulting from participation

Informed Consent

Additional Elements (continued)

4) Consequences to subject for decision to withdraw without orderly termination of participation
   - *Despite subject's right to withdraw, doing so may be difficult or dangerous, requiring tapering of drug or continued monitoring of procedure/surgery, etc*
5) Statement that significant findings developed during the course of the study which may affect subjects' willingness to participate will be provided
6) Approximate number of subjects to be enrolled

"I find it harder and harder to get any work done with all the ethicists hanging around."

Are human subjects of research adequately protected?

Despite these regulations, there are important aspects of this process that are not specifically mandated nor reviewed.

Beyond the mandates, *awareness and acceptance of the ethical principles* and guidelines regarding human subjects research should be applied by *individual researchers.*

Voluntariness

Voluntariness involves individuals making decisions that are their own (autonomous), free of excessive inappropriate external forces

External pressures can include emotional appeal from family members, pressure from clinician-researcher on patient, availability of treatment only through research, money

Distinction between **coercion and manipulation** - which impair voluntariness - and **persuasion**

Intentionality and Motivation

Intentionality =

making decisions based on individual goals and values

Willingness and Motivation =

- Altruism vs outside influence
- *Why* is the person volunteering?
- What do they expect or hope to get?

Recruiting and Obtaining Consent

Necessity to avoid “undue influence,” coercion, and manipulation

- Who should approach the potential subject and explain the research?
- Who should obtain consent?
- Under what circumstances?

Subject Selection

Eligibility and Suitability

- Must meet eligibility criteria for enrollment
- Will they follow procedures and comply with study protocols?
- Will they be honest with the researchers regarding non-compliance, adverse events, questions or problems with the research?

Understanding / Comprehension

Autonomous decisions must be grounded in sufficient understanding of relevant information

Conveying of information is NOT the same as assuring that is is understood

Distinction between general understanding and actual understanding - ie, appreciation of how the information applies to the individual

“Full” information may hinder understanding - consent form can represent information “overload”

Medical Practice vs Clinical Research

Many parallels, but not identical

- Motivation for participation - altruism and idealism versus personal benefit
- Choice versus voluntariness
- Likelihood of effect is unknown and unknowable without the research
- May be unknown and unforseeable risks

Moral Responsibilities of the Investigator

Mandated by Federal Regulations, Guided by Ethical Principles

- Respect for human subjects' ability to choose
- Absence of undue influence or coercion
- Provision of complete and accurate information at the level of comprehension
- Equitable treatment of human subjects
- Absence of conflict of interest

Protections for Human Subjects

Comments…

Thoughts…

Questions…