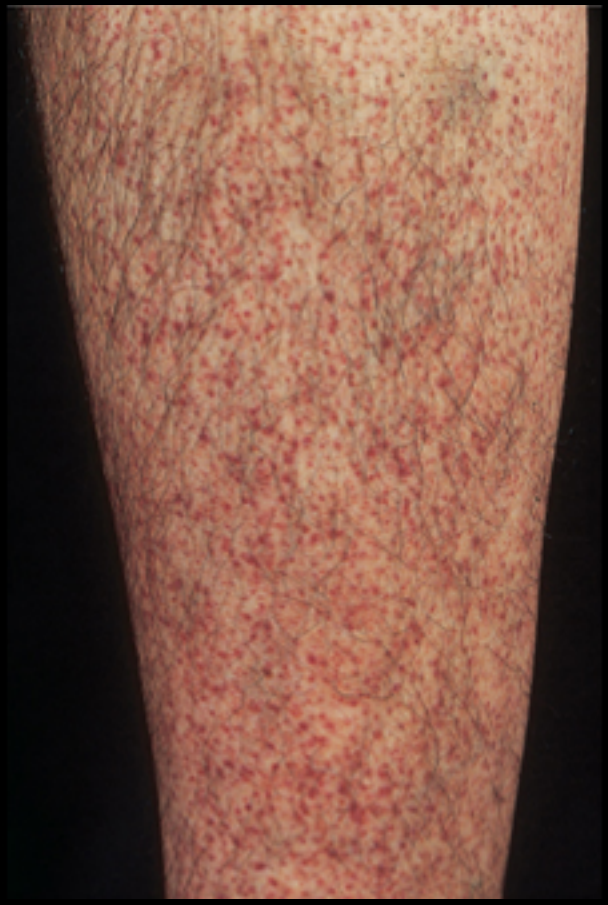
What Makes Research Ethical?
Rebirth of the ‘Integrated’ Model

David Wendler
Department of Bioethics
NIH Clinical Center

Disclaimer

The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or U.S. government.

Today’s Quiz



Scurvy

- 17th and 18th centuries: scurvy is killing many sailors.
- Different treatments are used without data on whether any are effective.

Clinical Trials

- 1747: James Lind, a British surgeon aboard the HMS Salisbury, conducts perhaps the first clinical trial in history.

- He divides 12 scurvy patients into six groups of two, and gives each group one of the existing treatments (one pair got citrus; another pair got sea water).

The ‘Integrated’ Model

- Lind’s experiment represents the beginning of an essentially 200-year history of conducting research in the context of providing clinical care.

- This ‘integrated’ model of clinical research has advantages: recruitment, efficiency, knowledge of subjects.

Conflicts of Interest

- Unfortunately, as history revealed, the conflict of interest inherent in the integrated model can lead to abuse.

- Tuskegee Syphilis Study: Clinicians ignore the medical needs of their patients in order to collect data.

The ‘Segregated’ Model

- In response to abuses, a “bright line” is drawn between research and care.

  Selby, Krumholz. *Hastings Center Report* 2013; 43: S34-S36

- This ‘segregated’ model separates research from care, raising the need for research specific guidelines.

Guidelines for ‘Segregated’ Clinical Research

Goals of Research

- The goal of clinical research is to generate information about human health and illness, and identify methods to prevent, diagnose and treat illness.

- Subjects are the *means* to gathering this information.

Benefits and Risks

- Participation in clinical research sometimes offers subjects the potential for medical benefit.
- Research interventions and studies also expose subjects to risks and burdens for the potential benefit of future patients.

Primary Ethical Concern

- The practice of exposing subjects to risks and burdens for the benefit of others raises the potential for exploitation.
- The many and extensive guidelines and policies for clinical research attempt to minimize this potential.

Nuremberg Code

- The Nuremberg trial of Nazi doctors after World War II led to the Nuremberg Code, which contains 10 basic principles for clinical research.

- The first principle states that voluntary consent is “essential” to ethical research.

Declaration of Helsinki

- Adopted by the WMA in 1964, modified seven times, most recently in 2013.
- Intended to address perceived shortcomings in Nuremberg, especially the need for independent review and the possibility of surrogate consent.

National Commission, 1974

- In response to Tuskegee, Congress establishes the National Commission, which issues the Belmont Report outlining the 3 principles of beneficence, respect for persons and justice.

- The work of the National Commission provides the basis for current US regulations for human subjects research.

ICH/GCP

- To harmonize drug development, Japan, Europe and the US agree to common guidelines.
- Extensive requirements on informed consent and guidelines on conducting clinical trials.

Comparison

- Existing guidelines were developed for specific reasons (e.g. response to past abuses, drug development).
- As a result, while there is a good deal of overlap, there are also differences and outright conflicts between the guidelines.

The 7 Principles Framework

Emanuel, Wendler, Grady. What makes clinical research ethical? JAMA. 2000;283:2701-11.

7 Ethical Requirements

1. Social Value
2. Scientific Validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for subjects

#1: Social Value

- The study should have the potential, typically together with data from other studies, to contribute to overall health and well-being.
- Results should be shared.

#1: Evaluation

- What treatments are currently available?
- How safe and effective are they?
- What is the value of a new treatment?
- What about the particular drug suggests it might offer added value?

This ethical evaluation requires scientific and clinical knowledge

#2: Scientific Validity

Design should answer the scientific question

- Include sufficient numbers, requisite comparison groups, necessary tests
- Appropriate lab studies
- Dose and duration of treatment, size and nature of sample, outcome measures

#2: Scientific Validity

- Study should be in a position to recruit a sufficient number of subjects and finish.
- Assessment of feasibility should consider
  - nature of the disease
  - community in question
  - resources available for the study
  - demands study places on subjects

#3 Fair Subject Selection

- Fair distribution of risks and potential benefits within and across communities
- No participant should be excluded without a good scientific or ethical reason

Start by assuming everyone is eligible

Evaluation

- What are the inclusion/exclusion criteria?
- What justifications are sufficient for exclusion?
- Is the inclusion of children justified?
- Are certain groups at higher risk of harm? Or more likely to benefit?

#4: Favorable Risk-Benefit Ratio

Step #1: Minimize risks

- Use qualified research team
- Eliminate duplicative procedures

Step #2: Enhance potential benefits

- Maximize scientific information
- Provide clinically relevant information

#4: Favorable Risk-Benefit Ratio

Step #3: Weigh risks against benefits: Do the potential benefits to subjects, if any, justify the risks they face?

Step #4: If yes: Study poses acceptable risks

If no: Are the ‘net’ risks acceptable and justified by the social value of the study?

#4: Favorable Risk-Benefit Ratio

- ‘Minimal’ net risks are typically acceptable.
- Greater net risks can be acceptable, but require greater justification and more safeguards.

#5: Independent Review

- Independent committee needs
  - Scientific, cultural, and ethical expertise
  - Authority to modify or stop the study

- Committee should provide initial and on-going assurance that ethical principles are met.

Centralized IRBs coming soon?

#6: Informed Consent

- Participants should understand
  - Their situation
  - The procedures, *risks*, potential benefits, and alternatives to research
- Participants should make a voluntary decision whether to enroll

Data: many subjects don’t give valid consent

Waiver

- Informed consent may be waived by the IRB when appropriate: risks are minimal, compelling reason to waive consent.

Incompetent Participants?

- Avoid enrolling individuals who are unable to consent
- Have safeguards in place when there is a compelling reason to enroll them
  - Surrogate
  - Assent

#7: Respect for Subjects

- Ethically sensitive research team
- Understand individuals and community
- Monitor subjects' welfare
- Right to withdrawal
- Turn subjects into participants

Conflicts

- In some cases, two or more principles may conflict.
- For example, adding procedures that increase scientific value may also increase risks (e.g. extra biopsy).

Resolving Conflicts

- In cases of conflict, decisions should be based on the relative importance of the competing considerations in the case.
- How great are the increased risks? How valuable is the added information? Can the subjects consent to the risks?

Expertise and Process

The need for judgment in making these determinations underscores the importance of knowledgeable and committed individuals, and an effective process, to ensure clinical research is ethical.

Rebirth of the Integrated Model of Clinical Research

Benefits

- The segregated model, with its extensive regulations and oversight, has been fairly effective at protecting research subjects.
- Comparatively few clear abuses or scandals in the past 30 years.

Problems

- However, the segregation of research and care, along with strict research regulations, has discouraged systematic efforts to capture data generated in the clinical setting.

- This is a real problem: clinical care generates countless data points, and we often don’t know what works.

LHC Systems

- Calls for learning health care (LHC) systems to address this problem.

- In LHC systems, the collection of data is “embedded into the core of the practice of medicine”.

Olson. The learning healthcare system: workshop summary 2007

Challenge

- LHC systems offer great potential to improve medical care.
- Challenge: managing the conflict of interest inherent in integrating research and care, and making sure that research remains ethical.

7 Ethical Requirements

1. Social Value
2. Scientific Validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for subjects

Application to LHC

- What kind of review is needed?
- When is consent necessary?
- What type of consent is sufficient?
- Coercion versus free riding?

Proposals

- LHC systems offer the opportunity to tailor review and consent to individual studies.

Largent, Joffe, Miller. *Hastings Center Report* 2011; 41:37-46

- Studies of low-risk interventions about which patients have no strong preferences do not need extensive consent.

Vickers, Scardino. *Trials* 2009; 10:14-21

SUPPORT Trial

- Standard practice for premature infants: maintain blood oxygen= 85%-95%.
- Unknown whether lower or higher levels within the standard range are better.
- Randomized infants to lower arm (85-89%) versus higher arm (91-95%).

SUPPORT Study Group. NEJM 2010; 362:1959-69.

Research and/or Care?

- The study underwent IRB review and parents provided consent for research.
- One view: there was no need to inform parents of any risks since all the infants were maintained with the standard range.

OHRP

- OHRP ruled that the study was risky and should have included a fairly detailed description of the risks.
- This finding has triggered widespread debate over what risks need to be disclosed.

45 CFR 46.116

"In seeking informed consent the following information shall be provided to each subject":

> "A description of any reasonably foreseeable risks or discomforts to the subject"

Example

- Study provides standard of care treatment and takes an extra skin biopsy for research purposes.
- Disclose the risks that research adds to subjects' lives: risks of the biopsy.

Comparative Effectiveness

- What risks do randomized studies of two approved treatments add to subjects' lives?
- What risks should be disclosed to obtain consent for research?

None

- Both treatments are approved and patients could get either one in the clinical setting.
- Hence, the research does not add any risks to subjects' lives and no risks need to be disclosed for research purposes.

All

- A subject randomized to treatment A might have gotten treatment B in clinical care (and vice versa).
- At time of consent, it is unknown whether subjects will receive A or B. Hence, the study might add either set of risks to the subject's life, suggesting that all the risks of both treatments need to be disclosed.

	mucosal lesions		rhabdomyolysis	congestive heart failure	hypoprothrombinemia		renal failure		papillary necrosis		
pancreatic cancer		conjunctivitis	Ringing in ears			pancreatic cancer				tachycardia	Ringing in ears
	Risk of fatigue	cerebral edema		Risk of bleeding				Risk of infection			
papillary necrosis			tachycardia	Risk of infection		Stomach pain				Risk of death	
		Risk of liver damage						Risk of neuropathy		cerebral edema	
Risk of bleeding		Angioedema	Ringing in ears		conjunctivitis	rhabdomyolysis	Stomach pain	hypoprothrombinemia		Risk of high blood pressure	
	hypoprothrombinemia		mucosal lesions		Risk of high blood pressure		cholestatic hepatitis		Angioedema		Stomach pain
Risk of clot		Risk of infection				tachycardia		Risk of clot		cerebral edema	congestive heart failure
	cholestatic hepatitis		congestive heart failure	Risk of liver damage			cholestatic hepatitis		pancreatic cancer	Risk of neuropathy	
Risk of death		Risk of high blood pressure		conjunctivitis		Risk of liver damage		papillary necrosis	rhabdomyolysis	renal failure	

Summary

- The 7 principles offer a framework for ensuring ethical clinical research.
- To realize the promise of LHC systems, while maintaining protection of subjects, future work will be needed to determine how to apply the framework to LHC systems.

Randomization

- Clinicians assign treatments to patients based on clinical judgment of what is best for the individual.

- Researchers frequently assign treatments to patients based on a random process.

Randomization and Risks

- It seems plausible to assume that randomization increases risks.

- Yet, data suggest that, in the setting of clinical equipoise, randomization is not associated with increased risks or decreased benefits.

Vist et al Cochrane Review 2008

Randomization and Risks

- In the setting of clinical equipoise, do patients need to be informed that treatments will be selected randomly?

YES

- Significant departure from standard of care.
- Many don’t want treatments selected randomly.
- Many want to know if randomized
- Clarifies that enrolled in research

No

- Randomization does not affect risks.
- Do not need to tell patients how choose treatments in the setting of clinical equipoise.
- May confuse subjects by suggesting greater risks