Reforming the Human Subjects Oversight System

Jeffrey R. Botkin, M.D., M.P.H.

Professor of Pediatrics

Chief, Division of Medical Ethics and Humanities

Associate Vice President for Research

THE UNIVERSITY OF UTAH

Disclosure

- I have no external financial interests that create a conflict of interest for this presentation

Our History

- **Henry K Beecher, MD: "Ethics and Clinical Research" NEJM, 1966.**
  - 22 examples of published studies in which investigators "endangered the health or the life of their subjects" without permission.
    - **Example 3: Chloramphenicol for typhoid fever: 23 additional subjects died in placebo control group**

Controversial Cases in Contemporary Human Subject Protections

- SUPPORT Trial
- Havasupai Tribe biospecimen research
- Residual newborn screening bloodspot research
- Jesse Gelsinger gene transfer trial
- International HIV trials
- Dan Markingson case
- Sham surgery trials

Contention

- The peer review system with IRB review and oversight of human subjects research has been extraordinarily successful
  - Virtually eliminating *systematic* breaches of ethical standards in the conduct of human subjects research
  - Standards have been largely incorporated into the fabric of research design and conduct
    - IRBs are not commonly disapproving protocols based on ethical concerns
    - Ethical issues remain but because ethical standards are uncertain in some contexts, not because investigators are breaching ethical standards
  - Exceptions exist (institutions and individuals)

Botkin, 2016

IRB Challenges

- Efficiency: the regulations permit substantial flexibility
  - A primary focus of the NPRM rather than efficacy
  - Limited investment => poor efficiency
  - Poor management => poor efficiency
- Efficient function
  - Use of electronic systems, appropriate staff support, and a focus on higher-risk/more complex protocols
- Supporting expert review
  - Obtaining domain-specific expertise for protocols
  - Expertise in the human subjects regulations

Botkin 2016

Challenges to Participant Engagement

- Long-standing recognition that informed consent in research is "broken"
  - The notion of breakage suggests that a functional process existed that has gone awry
  - Yet we have **NEVER** done an effective job with informed consent
- The interests of all stakeholders, save the participants, is served by complex consent forms and "efficient" processes

Botkin 2016

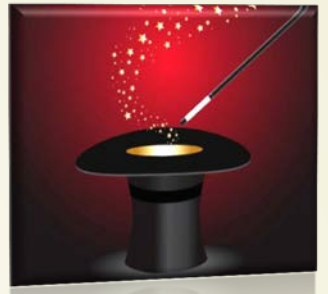
Comprehension

- Despite extensive evidence that research participants often have a very limited understanding of key elements of research protocols:

PEOPLE CONSENT TO PARTICIPATE IN RESEARCH ANYHOW!

Botkin 2016

Conclusions: Aiding Comprehension



- No magic: Poor comprehension and the "therapeutic misconception" remain common, serious concerns without adequate remedies
  - Revising forms for simplicity, processability, and graphical presentations is promising but with limited efficacy
  - Use of multimedia tools is promising
  - "Teach back" and one-on-one time are promising
- More research is essential: conceptual and empirical
  - Goal of developing methods to enhance comprehension, or
  - Goal of justifying why limited comprehension is acceptable

New Informed Consent Challenges

- Regulations designed in an era in which most research was conducted "at the bedside" through an interaction between the investigator and potential participant
- Increasingly now, research conducted by investigators who are removed from the participant in time and place, and large numbers of participants are required
  - Biospecimen research
  - Big Data research
  - Cluster randomized trials
- What is the appropriate role of individual informed consent in these contexts?
  - Should we focus on governance models that promote public awareness but do not rely on individual consent?

Botkin 2016

Other Challenges with Participant Engagement

- Research with individuals with impaired decision-making capacity
- A large gap in the federal research regulations
  - The gap is not addressed in the NPRM
- Will become increasingly important because:
  - Baby Boomers are aging
  - Innovative drugs and approaches to address neurocognitive impairments are coming

Individuals with impaired decision-making capacity

- Who should decide about research participation?
  - When can individuals decide for themselves?
    - May be project-specific given risks and complexity
  - Legally authorized representatives
    - State law variability and lack of state law
  - Assent by the participant
    - How to determine when assent is appropriate
    - How to make the assent process meaningful
  - Individuals with changing levels of capacity

Botkin 2016

Individuals with impaired decision-making capacity

- How much risk is appropriate for research without a prospect of benefit?
- SACHRP Recommendations (March 2009)
  - IRBs will ordinarily establish a lower threshold for acceptable risk in studies in which consent is provided by an LAR than in studies in which consent is provided by the participant him or herself. Standards for upper limits of allowable risk should be developed and applied. IRBs developing these standards should consider the following:
    a) In general, when the research offers little or no prospect of direct benefit, the probability and magnitude of harm or discomfort anticipated in the research (including, but not limited to, harm to physical, psychological, social or economic well-being and harms to dignity) should involve no more than a minor increase over minimal risk.
    b) In exceptional circumstances, an IRB may consider the approval of research which offers little or no prospect of direct benefit and in which the risk of harm or discomfort anticipated in the research is moderate in terms of probability and magnitude. In such cases, the research must include safeguards appropriate to this degree of risk. Furthermore, the research must be of vital importance in the understanding, prevention or alleviation of a serious problem affecting the health or welfare of the study population.

Investigator Integrity

- Human subject protections depend on the integrity of the investigator
  - A basic understanding of ethical standards in research
  - Compliance with ethical and regulatory requirements
  - Ethical decisions when unusual circumstances arise “in the trenches”
- One of the most serious threats to human subject protections is investigators who lack integrity
  - Investigators who are serial violators of rules and expectations
- Not addressed in the NPRM

Investigator Integrity

- Federal regulations govern **institutions** that receive federal dollars for research
- The federal regulations in the Common Rule have virtually no specific expectations for investigators
- Presidential Commission: **"*MORAL SCIENCE: Protecting Participants in Human Subjects Research*,"** recommended that *"The Common Rule should be revised to include a section directly addressing the responsibilities of investigators. Doing so would bring it into harmony with the Food and Drug Administration regulations for clinical research and international standards that make the obligations of individual researchers more explicit, and contribute to building a stronger culture of responsibility among investigators."*

Botkin 2016

SACHRP Recommendations (Jan 2013)

- SACHRP proposes the addition to 45 CFR 46 of three sections that would cover, at a minimum:

  (1) responsibilities of investigators;

  (2) qualification standards for investigators (e.g., training); and
  (3) investigator documentation/records.

- New regulations to ensure investigator accountability would codify the current ethical expectations for investigators who conduct research involving human subjects. Regulations addressing investigator responsibility should emphasize the critical role of the investigator and hold the investigator directly accountable for his/her actions.

Investigator Integrity

- A large proportion of serious issues arise from repeat offenders
- Work necessary on how research institutions should address investigators with a track record of serious non-compliance
  - Non-compliant studies can be adequately addressed currently
  - To what extent can investigators be limited prospectively?
  - To what extent can compliant studies be restricted due to non-compliance in other studies?
  - Academic freedom issues

Botkin 2016

Beyond Oversight

- Greatest threats to participant welfare may come from poorly designed research that does not contribute to public welfare
  - Research results that cannot be reproduced
    - NIH initiative for rigor and transparency
    - Enhanced education for clinical scientists
  - Role of industry in the design and conduct of clinical research

Thank You!