

Ethics and Safety in Human Subjects Research

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Background and Disclosure

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Ph.D. Health Care Ethics, M.A. in Biomedical Ethics and Health Care Policy, M.Ed. in College Student Personnel – Administration.

In health care for over eight years.

I do not have any financial interests in this topic. I am a member of an Institutional Review Board as well as a Research Oversight Committee.



Ethical Duties

- Practice – *Principles of Biomedical Ethics*, Beauchamp and Childress
 1. Autonomy (respect for)
 2. Beneficence
 3. Nonmaleficence
 4. Justice
- Research – Declaration of Helsinki, Belmont Report, 45 CFR 46, 21 CFR 50
 1. Autonomy (respect for)
 2. Beneficence
 3. Justice
 4. Safety
 5. Privacy (respect and protection)

Nurses' Duties to Safety – ANA Code of Ethics

- 1.5 “Nurses value the distinctive contribution of individuals or groups as they seek to achieve safe, quality patient outcomes in all settings.”
- 3.4 “Nurses must participate in the development, implementation, and review of and adherence to policies that promote patient health and safety, reduce errors and waste, and establish and sustain a culture of safety.”
- 3.5 “Nurses must be alert to and must take appropriate action in all instances of incompetent, unethical, illegal, or impaired practice or actions that place the rights or best interests of the patient in jeopardy...When incompetent, unethical, illegal, or impaired practice is not corrected and continues to jeopardize patient well-being and safety, nurses must report the problem...”
- 5.4 “...Nurses are obligated to provide for patient safety...”

Safety Duties in Research – Specified

- Identify risks and potential risks
- Design interventions to mitigate risks
- Screen during the study for adverse events and prepare to stop it if needed

Source: Adams, Lizbeth and Timothy Callahan. (2013). Research ethics. In *Ethics in Medicine*. Seattle, WA: University of Washington School of Medicine. Available at <https://depts.Washington.edu/bioethx/topics/resrch.html>.

- Ascertain potential and participants who may have higher than usual risk
- Careful informed consent, disclosing and discussing risks and alternatives
- Consider any other responsibilities (e.g., rollout care, ancillary care, and/or sample storage and banking)
- Know your community and populations

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The science of safety is now playing an important role in clinical medicine, yet it has not been as closely incorporated into the conduct of clinical and translational research.

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Source: Sugarman, Jeremy. (2013). Maximizing safety in clinical and translational research. *IRB Ethics & Human Research*, 35(1): 16.

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The primary concern of the investigator should be the safety of the research participants.

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Source: Adams, Lizbeth and Timothy Callahan. (2013). Research ethics. In *Ethics in Medicine*. University of Washington School of Medicine. Available on-line at <https://depts.washington.edu/bioethx/topics/resrch.html>.

Ascertain Higher Risks – Vulnerability

Types of vulnerability:

- Cognitive – Is not only “degrees of immaturity, dementia, mental illness,” and so on, but “educational deficits, unfamiliarity with the language,” and accelerated timeframes.
- Juridic – Is some type of relegation to the power of another, and it includes children, students, prisoners, soldiers, and others.
- Deferential – Portrays circumstantial relegation to the influence of another, often a certain other person, and participants or candidates may have juridic vulnerability (e.g., children not wanting to argue with a parent) or not (e.g., in some cultures, women defer to men).

Source: Kipnis, Kenneth. (2001). Vulnerability in research subjects: A bioethical taxonomy. *Ethical and Policy Issues Involving Human Participants, Volume II: Commissioned Papers and Staff Templates*: G-7 – G-8.

Ascertain Higher Risks – Vulnerability

Types of vulnerability, continued:

- Medical – Describes a participant or candidate with a “serious health-related condition for which there are no satisfactory remedies,” such as end-stage AIDS or cancer, causing the person to take risks she or he usually would not.
- Allocational – Persons require basic needs or goods such as money, shelter, or health care, which should prompt evaluation, albeit difficult, of exploitation.
- Infrastructural – Is not having available the “protections and resources that contribute importantly to the safety of the research subject,” such as a computer with (high-speed) internet access, a refrigerator, or even consistent electricity.

Source: Kipnis, Kenneth. (2001). Vulnerability in research subjects: A bioethical taxonomy. *Ethical and Policy Issues Involving Human Participants, Volume II: Commissioned Papers and Staff Templates*: G-8 – G-12.

Ascertain Higher Risks – Vulnerability

- Are potential participants vulnerable in the same ways? Is there nuance to vulnerability?
- How do we respond to the potential inclusion, or not, of vulnerable groups? What should we do?
- Are there consequences of not including vulnerable persons in research? If so, what are they?

Ascertain Higher Risks – Vulnerability

Be aware but go beyond the baseline, articulated in documents such as:

1. The *Belmont Report* – names some vulnerable populations, available at <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>
2. Federal Regulations on the Protection of Human Subjects (45 CFR 46) – regulations about some vulnerable populations, available at <http://www.hhs.gov/ohrp/policy/ohrpreulations.pdf>
3. The *Final Report* of the Advisory Committee on Human Radiation Experiments – advises particular protections, available at <https://www.osti.gov/opennet/servlets/purl/120931/120931.pdf>

Source: Kipnis, Kenneth. (2001). Vulnerability in research subjects: A bioethical taxonomy. *Ethical and Policy Issues Involving Human Participants, Volume II: Commissioned Papers and Staff Templates: G-3.*

Identify Risks – Conflicts-of-Interest

Different types of conflicts-of-interest exist:

- A. Primary – For clinicians in research, they are patients' health and research integrity for current and future participants.
- B. Secondary – Conflicts are around personal wellbeing, when these interests manipulate decisions around primary interests.
- C. Financial – A researcher (potentially) receives a monetary benefit, especially for particular enrollment (per capita or finder's fees) or results.
- D. Non-financial – A researcher (potentially) gains other benefits from research, such as prestige, career advancement, or other “creature comforts.”

Source: Goldner, Jesse. (2000). Dealing with conflicts of interest in biomedical research: IRB oversight as the next best solution to the abolitionist approach. *Journal of Law, Medicine, and Ethics*, 28(4): 380-384.

Identify Risks – Conflicts-of-Interest

Different types of conflicts-of-interest exist:

- E. Individual – A researcher has a study where she or he (potentially) receives benefit.
- F. Institutional (Organizational) – Organizations, often academic medical centers, find themselves caught between the polarities of wanting to improve clinical care and financially benefiting from research and its sponsorship.

Source: Goldner, Jesse. (2000). Dealing with conflicts of interest in biomedical research: IRB oversight as the next best solution to the abolitionist approach. *Journal of Law, Medicine, and Ethics*, 28(4): 381-385.

Arguably, the goal of universities is to seek the truth while the goal of (pharmaceutical) companies is to make money.

Source: Schafer, Arthur. (2004). Biomedical conflicts of interest: A defense of the sequestration thesis – learning from the cases of Nancy Olivieri and David Healy. *Journal of Medical Ethics*, 30: 9.

Identify Risks – Conflicts-of-Interest

- What is the difference between actual and potential (perceptual) conflicts-of-interest? Do both actual and potential conflicts-of-interest deserve attention? Why? What may result from potential (perceptual) conflicts-of-interest?
- Could actual or potential conflicts-of-interest compromise patient safety? How?
- Is using a corporate sponsor for research inherently unethical? Why or why not?

Mitigate Risks – Conflicts-of-Interest

Stakeholder and Role	Obligation or Duty
Researcher	Respect autonomy, nonmaleficence, justice, disclose, transparency, safety
University	Monitor and analyze, scholarship
Corporate sponsor	Financial interest in contract and results
Participant	Informed consent (appreciate info, clarify questions, etc.), transparency and candor, confidentiality, responsibility

Based on source: Estroff, Sue. (1999). The gaze of scholars and subjects: Roles, relationships, and obligations in ethnographic research. In *Beyond Regulations: Ethics in Human Subjects Research*, Nancy King, Gail Henderson, and Jane Stein, editors. Chapel Hill, NC: The University of North Carolina Press, 77.

Mitigate Risks – Conflicts-of-Interest

- Make researchers' integrity a priority
- Complete and full disclosure

Source: Kopelman, Loretta. (1999). Bias and conflicts of interest in science: Controversial industry funding of infant-feeding studies. In *Beyond Regulations: Ethics in Human Subjects Research*. Chapel Hill, NC: The University of North Carolina Press, 127.

- Separate the clinician-researcher roles
 - Clinician dyad
 - Third party

Source: Levine, Richard. (1992). Clinical trials and physicians as double agents. *Yale Journal of Biology and Medicine*, 65: 72.

Screen for Adverse Events – Ability to Respond

Does the timing for study enrollment matter? Consider the following examples:

- TGN₁₄₁₂ – Is a “genetically engineered anti-CD28 antibody” used to expand T cells, possibly having therapeutic benefit for those with autoimmune conditions such as rheumatoid arthritis. Animal studies did not raise concerns and established dosing for phase I clinical trials with human subjects. However, a TGN₁₄₁₂ infusion, 500x smaller than animal doses, caused a “life-threatening ‘cytokine storm’” and multiple organ system failure in the first six, healthy, human volunteers. All six participants received TGN₁₄₁₂ within 90 min. of one another, such that the first volunteer experienced symptoms as the last was being infused.

Source: Attarwala, Husein. (2010). TGN1412: From discovery to disaster. *Journal of Young Pharmacists*, 2(3): 332-336; Sugarman, Maximizing safety, 15.

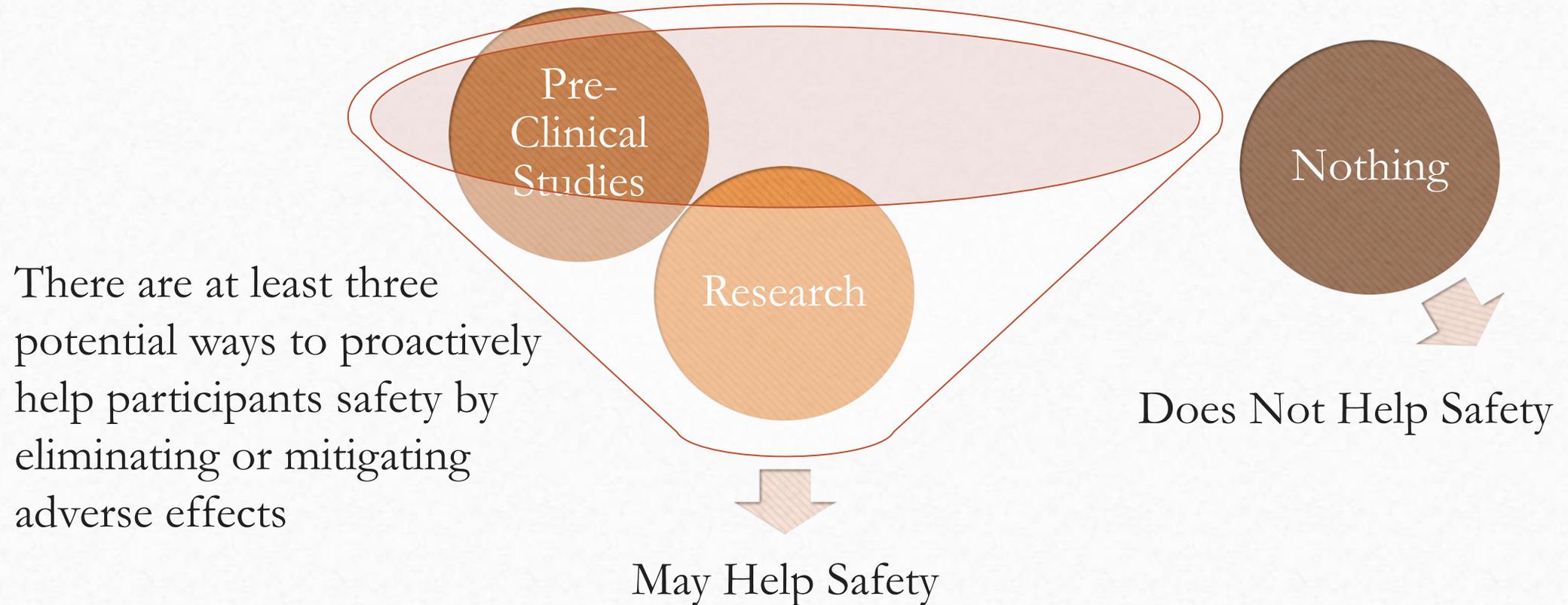
Screen for Adverse Events – Ability to Respond

- TriA (triacetylolandomycin) – Evidences hepatic dysfunction, yet a dosing study proceeded with 50 “participants” (healthy 13- to 39-year-olds, including those with cognitive disabilities, incarcerated youths). Within two weeks, 54 percent had “abnormal excretion of bromsulfalein” and 8 patients had marked dysfunction with biopsies confirming liver damage.

Source: Beecher, Henry. (2001). Ethics and clinical research. In *Medical Ethics: Applying Theories and Principles to the Patient Encounter*, Matt Weinberg editor. Amherst, NY: Prometheus Books, 531.

What can we learn?

Mitigating Adverse Events – Potential Options



Mitigating Adverse Events – TGN₁₄₁₂ Responses



Careful Informed Consent – Considerations

What are the ethical elements necessary for appropriate informed consent?

Careful Informed Consent – Considerations

What to avoid:

- Being nebulous about possible benefits
- Misrepresenting treatment, making research seem like treatment
- Shifting and unclear terms

Source: King, Nancy et al. (2005). Consent forms and the therapeutic misconception. *IRB Ethics & Human Research*, 27(1): 6.

- Conceptualizing informed consent as an event rather than a process
- Concentrating on the consent form itself

Source: Berg, JW, Appelbaum, Paul et al. (2001). *Informed Consent: Legal Theory and Clinical Practice*. New York, NY: Oxford University Press, 295.

- Industry terms, medical jargon, technobabble

Careful Informed Consent – Considerations

What to do or consider:

- If possible, slow down the assimilation of new information: ask questions after review of the written documents, provide further info, schedule follow-up
- Balance “clarity with brevity” in the document; reading level
- Discussion groups with participants who have gone through the research
- Questionnaires to assess knowledge and comprehension before consent
- Differentiate research from clinical care, being specific about dissimilarities

Source: Berg, JW, Appelbaum, Paul et al. (2001). *Informed Consent: Legal Theory and Clinical Practice*. New York, NY: Oxford University Press, 291-299.

- Use a “trained, neutral educator (nurses are natural candidates)”

Source: Appelbaum, Paul, Roth, Lauren, Lidz, Charles, Benson, Paul and William Winslade. (1987). False hopes and best data: Consent to research and the therapeutic misconception. *Hastings Center Report*, 17(2): 24.

Careful Informed Consent – Considerations

What to do or consider, continued:

- Who discusses informed consent? Depending on the study, 47-70% have a principal investigator involved in informed consent, with many delegating it to assistants. Does this show investigators do not hold consent in high regard?
 - What are the understandings of the assistants? What standards are they held to, meaning are there expectations of enrolling a certain number of participants?
 - To what extent do principal investigators monitor assistants?

Source: Berg, JW, Appelbaum, Paul et al. (2001). *Informed Consent: Legal Theory and Clinical Practice*. New York, NY: Oxford University Press, 290.

Other Responsibilities

Ancillary care – “Is [an understanding] which goes beyond the requirements of scientific validity, safety, keeping promises, or rectifying injuries.”

Source: Richardson, Henry and Leah Belsky. (2004). The ancillary-care responsibilities of medical researchers: An ethical framework for thinking about the clinical care that researchers owe their subjects. *Hastings Center Report*, 34(1): 26.

Rollout care – Is a subset of ancillary care related to the types of care needed, if any, for participants after the conclusion of the study.

Sample storage and banking – Is the treatment of human samples (e.g., tissue, DNA), not just during, but after the conclusion of a study

– *The Immortal Life of Henrietta Lacks* by Rebecca Skloot

Other Responsibilities

The scholarly community does not have agreement about obligations for ancillary and rollout care. The graph below represents the tensions between views.



How would you describe the differences between above views?

Some propose a framework for what qualifies for research support and what does not.

Source: Richardson, Henry and Leah Belsky. (2004). The ancillary-care responsibilities of medical researchers: An ethical framework for thinking about the clinical care that researchers owe their subjects. *Hastings Center Report*, 34(1): 26-27.

Other Responsibilities

Duty to Warn

- What about discovering information about a condition or disease during a research study? Think about genetic research.

	Study-Related Genes		Study-Unrelated Genes	
	Express	Carrier	Express	Carrier
Participant	?	?	?	?
Offspring and siblings	?	?	?	?

- What about indefinitely storing samples for any future research purpose while asking participants to give up all rights?

Community and Populations

A few words about understanding culture...

An ethnographic study of Vietnamese Americans in Orange County, CA found factors associated with adherence (compliance) with a TB treatment. Medicines associated with feeling imbalanced or incongruent, “feeling hot,” the influence of advocates (family, friends), and community perception all influenced adherence in this community.

Ito, Karen. (1999). Health culture and the clinical encounter: Vietnamese refugees' responses to preventive drug treatment of inactive tuberculosis. *Medical Anthropology Quarterly*, 13(3): 338-364.

Situation: How could this study impact research on a new TB treatment with a similar chemical properties and pathways within the same community?

Community and Populations

Consulting with a community group has several purposes:

- A. It is a bridge between researchers and the population being investigated
- B. Communicate any community or cultural concerns
- C. Aid the creation of study-related resources
- D. Support vulnerable groups and their rights; help groups with stigma
- E. Provide suggestions for participants' study enrollment
- F. Develop trust through open communication
- G. Look for indications about harm to the community

Quinn, Sandra. (2004). Protecting human subjects: The role of community advisory boards. *American Journal of Public Health, 94*(6): 918: Strauss, Ronald. (1999). Community advisory board – Investigator relationships in community-based HIV/AIDS research. In *Beyond Regulations: Ethics in Human Subjects Research*. Chapel Hill, NC: The University of North Carolina Press, 94-99.

Case Study and Questions
