1: Basics of Research Ethics, History of Research Ethics and the Concept of Risk

Basics in Research Ethics:

History of research ethics and the concept of "Risk"

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What events come to mind when you think of the modern history of research involving human participants? Are there special considerations for children?

This module summarizes milestones in the history of research ethics, with a particular emphasis on research involving children and vulnerable populations, and provides an introduction to the ethical analysis of "risk."

The objectives of this chapter are threefold:

- Recognize the centrality of voluntary consent in human research.
- Identify the ethical concerns with third-party (surrogate) decision-making regarding acceptable risk.
- Describe the different conceptions of risk for child participants.

History

The Nuremberg Trials

In 1947, 23 Nazi physicians and medical administrators were found guilty on charges of "murders, tortures and other atrocities committed in the name of medical science." The tribunal recognized that certain types of medical experiments were ethically justified but, delineated "basic principles that must be observed in order to satisfy moral, ethical and legal concepts." These points have become known as the Nuremberg Code:

- The voluntary consent of the human subject: the person involved… should be so situated as to be able to exercise free power of choice without the intervention of any element of force, deceit… or any form of coercion.
- Experimental validity: the experiment should be such as to yield fruitful results for the good of society.
- Other principles: avoidance of unnecessary harm and the importance of scientifically qualified researchers.

The trial of physicians at Nuremberg anticipated a major challenge to the Hippocratic tradition, which states that physicians should not inflict "intentional harm or injustice." As scientific medicine developed, it was clear that new treatments would have to be studied in real patients who may be harmed with no hope for benefit before we would have evidence of the balance of potential benefits and risks. Thus began the ethics of human experimentation.

Tuskegee

In 1972 it was revealed that for 40 years the US Public Health Service had been performing studies on poor black men from Tuskegee, Alabama who had been denied treatment for syphilis. Awareness of these studies created a demand for more stringent regulations regarding informed and voluntary participation in human research.

The Need for Research in Vulnerable Populations

One might suggest that research should only be done on consenting adults who can make choices about risks, harms, and benefits, and that this research information should be then extrapolated to children and other populations. The history of research demonstrates clearly that this course has frequently been dangerous in its misunderstanding of the unique nature of the growing and developing child. The Nuremberg Code in its insistence on voluntary research participation prohibited most research involving children and many vulnerable populations. The Declaration of Helsinki formally disallowed non-therapeutic research on non-consenting subjects. Both of these codes present difficulties for those who work to advance the health of the most vulnerable in society, including children, who have not yet achieved the capacity for consent, and adults who have temporarily or permanently lost this capacity.

An essential and enduring problem for society is how to promote the best interests of children and other vulnerable populations through participation in research advances while protecting their rights and welfare.

It should be clear that while voluntary participation is an essential value, those who are not capable of giving voluntary consent must be studied somehow so they too can benefit from scientific advances. Policy that strictly prohibits children and other vulnerable populations from participation in research may harm both individuals and the populations en masse by making them research "orphans." Overprotection can be harmful.

Concept of Risk

The conduct of clinical research is responsible for upholding three central ethical principles: respect for persons, beneficence, and justice. These principles are codified in the US Federal Common Rule and many international research guidelines, including the Canadian Tri-Council Policy Statement. One principle of respect for persons requires that those who are unable to consent have protections, including a surrogate decision-maker. In the case of a child, the parent usually adopts this role as it is assumed that they act in the best interests of the child. In addition, respect requires a promise of confidentiality. The principles of non-maleficence and beneficence follow two complementary tracts: to do no harm and to maximize potential benefits while

minimizing risk. Research ethics committees are charged with examining studies to determine whether or not there is an acceptable balance of risk and potential benefit. This is particularly true for participants who are vulnerable, such as children, and others who have a diminished capacity for decision-making. Lastly, the principle of justice requires that the burdens of research participation are distributed equally and, in addition, the potential benefits of research are accessible to all. Thus, there is a tension between offering

protection to potentially vulnerable subjects such as children and ensuring that they have equitable access to advancements in science, which are only available through carefully conducted research.

Definitions of Minimal Risk

The US Federal Common Rule describes minimal risk as meaning that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Both the Canadian Tri-Council Policy on Research and the US Common Rule provide a limited list of minimal risk procedures and activities. The concept of minimal risk should also be considered in the overall context of the research. For example, a single venipuncture may not constitute more than minimal risk but a protocol that requires multiple venipunctures may well exceed what is considered minimal risk. It is also important to recognize that context may play an important role in interpreting minimal risk. For example, does minimal risk mean a) all the risks normal people encounter, b) the risks all healthy normal people encounter, or c) the minimal risks all healthy normal people encounter? Each of these interpretations has difficulties. Exposure to risk varies depending upon occupation, lifestyle, and habits, from the accountant working from home to the cliff-diving firefighter. Clearly, some of these life experiences constitute significant rather than minimal risk. If we consider what all people may be exposed to, we get into difficulty defining what is likely for whom, as well as how it applies across cultures and geographic locations. The magnitude of risk of exposure in one setting may be quite different from that of another, yet both constitute normal day-to-day exposures.

The US Common Rule further defines minimal risk as that which may be encountered in regular health care interactions. However, there is difficulty in interpreting what is "normally encountered." While some invasive procedures may be easily ruled out as more than minimal risk, debate continues on what the cutoff should be. In addition, it is important to avoid focusing exclusively on the physical; we must not overlook psychological, social, and economic risks. Each should be included in the wide spectrum that is examined by research ethics committees.

Risk in Therapeutic Procedures

Risks involved in therapeutic procedures should be evaluated separately from the risks of non-therapeutic procedures since treatment itself may constitute considerable risk of harm. Therapeutic risks could be regarded as falling within the range of minimal risks for research participants as they are an inherent part of the patient's treatment. The test in this situation is the principle of clinical equipoise. This exists when there is a state of uncertainty within the expert

clinical community as to the relative superiority of two strategies of treatment. This is based on the premise that, regarding the anticipated balance between harms and benefits, the intervention being tested is standard. Therefore, exposure to therapeutic risk even in vulnerable subjects is acceptable as long as a situation of clinical equipoise exists. Thus, ethicists have argued that an ethical analysis of risk would set no limit on the therapeutic risk to which children may be exposed. Indeed, this is the case in which children with cancer are exposed to chemotherapy agents in which death, secondary to toxicity of treatment, is a real and not infrequent event. This would only be acceptable in a research context if clinical equipoise existed.

Non-therapeutic Procedures

Non-therapeutic risks are those actions that go beyond the needs of the subject and occur only for the benefit of the research project. Thus, it is important for a research ethics committee to distinguish therapeutic from non-therapeutic research in determining the overall acceptability of the research. Research ethics committees should total up the accumulative additional research risk that a given study poses to children in determining where it stands in the minimal risk to potential benefits ratio.

Two main ethical requirements underline the acceptability of non-therapeutic procedures, that risk should be minimized and that risks posed by non-therapeutic procedures should be proportional to the knowledge that may be reasonably expected to be gained. Thus there is a limit to the magnitude of non-therapeutic risk to which the subject may be exposed. The research ethics committee has several important roles. One is to disallow a procedure if there is a less invasive alternative. A second is to question the inclusion of procedures that do not lead to creation of important new knowledge when there may be potential harm.

Third-party Decision-making

When an individual is incapable of providing his or her own consent, we must obtain consent from a third party decision-maker. In general, this is the responsibility of parents or guardians who are generally regarded to have the best interest of the individual child in mind.

There are, however, a variety of vulnerabilities when adults make decisions for children, in particular where significant disease is present in a child. Potential conflict of interest in determining the competence of an adolescent to make a research decision may be present for the parent. There may also be significant influence by health care professionals who are also investigators or recruiters for research protocols, especially if the disease is rare and the parent has no other choice for medical care. A third-party decision-maker who is under pressure may allow greater risk in defining acceptable minimal risk than would an impartial observer. This must be considered by the researcher in designing research projects and by the research ethics committees in assessing for acceptability. This applies for children, as well as for other vulnerable populations such as adults with dementia. It would be unethical for a legal proxy to authorize a patient's participation in research that represented more than a minor increment over minimal risk, unless there was anticipated potential direct benefit for that individual. The proxy must also withdraw the subject's participation if unacceptable or unforeseen harms or discomforts begin to accrue. A simple example of this is an immunization study with regular

blood monitoring where a child becomes increasingly distraught with follow-up blood work for serology. In this situation, it would be appropriate for the parent to withdraw the child from the study.

Placebo-controlled Trials

As placebo-controlled trials are widely regarded as a gold standard for testing, this methodology may well be applied to children's research. The ethics of placebo controlled trials remains controversial. Miller et al. have outlined an approach to considering the acceptability of placebo-controlled trials by stating that placebo controls and active treatment should be evaluated as separate interventions. As such, the risk/benefit profiles should be assessed independently for each arm of a study involving placebos. They argue that the clinical trials may only be approved

when the placebo intervention satisfies one of three conditions: 1) minimal risk, 2) greater than minimal risk but with the prospect of direct benefit from the placebo intervention (and at least as favourable as the available alternatives), or 3) a minor increase over minimal risk if direct benefit from the placebo is unlikely but the study is deemed likely to produce knowledge of vital importance to the subject's own condition or disease. In addition, the placebo control should be approved only if there are convincing methodological reasons to use them rather than an active control.

The concept of minimal risk has two main functions. The first is to help focus a research ethics committee's attention on studies that involve more than minimal, non-therapeutic risk. It thus allows an expedited review of minimal risk protocols – the foundation of proportionate review. In this function, it also allows that risk is more than just physical and that, for example, secondary use of data may represent more than minimal risk and require informed consent, either of the original participants or a community representative. The second major function of defining minimal risk is to guide the acceptability of studying or exposing persons incapable of giving consent, including children. Risk analysis underpins these two crucial functions.

Key Points

- Research involving infants and children and adolescents must be undertaken to provide them the same potential benefits as adults.
- The concept of risk in this population must include a consideration of minimal risk for non-therapeutic research.
- There is no moral reason to exclude high risks in therapeutic research as long as there is clinical equipoise.
- The definition of minimal risk is contextual.

Links

- Ethics and Regulation of Research with Children
  http://www.ehcca.com/presentations/ressummit3/2_04.pdf

- Integrity Advisory Panel on Research Ethics (Canada)
  http://www.pre.ethics.gc.ca/english/index.cfm

- The Canadian Tri-Council Policy Statement on Research Ethics. Section on Minimal Risk, Section 1, C1
  http://www.pre.ethics.gc.ca/english/policystatement/policystatement.cfm

- The Interactive Research Training Curriculum, Web Version
  http://www.fhi.org/en/topics/ethics/curriculum/default.htm

- The Belmont Report. Ethical Principles and Guidelines for the Protection of Human Subjects of Research **http://ohsr.od.nih.gov/guidelines/belmont.html**