ethical decision-making in the context of human research

*Ethical Challenges in Medical Decision Making*
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**Learning objectives**

- Understand the scope of Kaiser Permanente’s research program.
- Have the ability to differentiate between the underlying motivations of clinical therapy and clinical research, and understand how this can lead to conflicting goals on the part of the clinician/researcher.
- Better understand the therapeutic misconception and the role it plays in research.
- Have the ability to describe the ethical and intellectual challenges faced by clinician/researchers in explaining research and its aims to potential participants (the informed consent process), and the challenges faced by participants in their understanding of research.

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**Topics we will discuss**

- Research at KP
- Ethical, regulatory, and policy foundations of clinical research
- Clinical medicine and clinical research
- The therapeutic misconception
- Informed consent in research
- Special issues with pediatric clinical trials

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**Research at KP**

- Programwide:
  - There are 2,200 human research studies currently open, with a large regional variation, from fewer than 50 to more than 1,100.
  - 425,000 KP members participate in clinical trials.
  - There are two communities of researchers: those in regional research centers, and clinicians located in healthcare facilities. Approximately 2,000 investigators are engaged in research.
  - Research worth $125 million annually is conducted.
  - The research undertaken is a mix of clinical trials, health services research, and epidemiological studies. Basic science research is not conducted.

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**Research in Northern California/TPMG**

- The TPMG/KPNC research program is KP's largest, with 1,154 active studies.
- The Division of Research is home to 51 investigators, who authored 162 peer-reviewed papers in 2008. DOR has a total staff of 469. In 2008, its funding was $72.8 million.
- About 750 principal and co-investigators are also located at facilities throughout the region.
- Of the 1154 active projects, 347 (30.1%) are FDA-regulated clinical trials.
- Of the 347 clinical trials, 44 (12.7%) are Phase II trials, and 303 are Phase III or IV. KP generally does not conduct Phase I clinical trials.

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**Kaiser Foundation Research Institute**

- KFRI, a part of Program Office Community Benefit, was founded in 1958. KFRI is the national KP office responsible for human subjects research compliance and research ethics. We carry out our compliance and ethics efforts in conjunction with the eight operating Regions and PMGs.
- Institutional Review Boards
- HIPAA privacy and security in research
- Responsible conduct of research
- Conflicts of interest in research
- Good clinical practice
- Federal grant administration and finance
Research is characterized by a high degree of regulation

- Researchers are expected to follow the rules.
  - Food and Drug Administration
  - Office for Human Research Protections
  - Office of Research Integrity
  - Office for Civil Rights
  - Good Clinical Practices from the International Committee on Harmonisation
  - Various state regulations

Nazi Germany’s “medical experiments”

Nazi Germany’s “medical experiments”

Josef Mengele, German physician and SS captain.

Tuskegee Syphilis Study

The United States government did something that was wrong - deeply, profoundly, morally wrong. It was an outrage to our commitment to integrity and equality for all our citizens...

The American people are sorry for the loss, for the years of hurt. You did nothing wrong, but you were grievously wronged. I apologize and I am sorry that this apology has been so long in coming.

President William J. Clinton, May 16, 1997

Jewish Chronic Disease Hospital

The protocol involved injecting a culture of cancer cells under the skin of elderly, disabled patients with compromised immune systems, without first having obtained informed consent.
Gene therapy

Jesse Gelsinger, 1981-1999

Gelsinger had a relatively mild form of a genetic enzyme deficiency which impaired urea formation and produced ammonia in his blood.

He died as a direct result of his participation in a gene therapy clinical trial, in which the Principal Investigator had a significant financial conflict of interest.

Conflicts of interest

Charles B. Nemeroff, MD, earned more than $2.8 million in consulting arrangements with drug makers from 2000 to 2007, failed to report at least $1.2 million of that income to Emory University and violated federal research rules, according to documents provided to Congressional investigators.

Joseph Biederman MD, a world-renowned child psychiatrist at Harvard Medical School and Massachusetts General Hospital, had failed to report to Harvard at least $1.4 million in income from drug companies, in violation of the university’s conflict-of-interest guidelines.

Ethical foundations of clinical research

Nuremberg Code (1947)

"The voluntary consent of the human subject is absolutely essential."

Ethical foundations of clinical research

Declaration of Helsinki (1964)

“In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.”

Ethical foundations of clinical research

Belmont Report (1979)

• Three Principles
  • Respect for Persons: Requires recognition of the personal dignity and autonomy of individuals and the need for special protections for people with diminished autonomy (e.g., vulnerable populations).
  • Beneficence: Requires that all appropriate steps be taken to protect potential research volunteers by minimizing possible risks of harm and maximizing potential benefits.
  • Justice: Requires that the benefits and burdens of research be distributed fairly among potential research participants.

Kaiser Permanente Policy

The KP Human Research Participant Protection Program defines the authority and responsibilities of positions and entities that play key roles in protecting the welfare, rights, and safety of participants in research at KP.
Institutional Review Boards

- IRBs are institutional committees that formally approve proposed, and have oversight of ongoing, human subjects research.
- IRBs look at the science, the ethics, and the regulatory aspects of human subjects research.
- IRBs operate independently of the institution.

Integrity of the researcher

In the final analysis, the integrity of researchers to both the process of research, and to those individuals who participate in research, is the cornerstone of the overall success of the research endeavor at KP.

Clinical medicine is not clinical research

- In the clinician-patient relationship, the interaction is patient-focused, with the goal of curing the patient, or at least minimizing suffering and maximizing quality of life, if a cure is not possible.
- In the researcher-participant relationship, the interaction is focused on the development of generalizable knowledge.

Professional integrity in clinical research

“The professional integrity of the physician investigator depends on a coherent moral identity that is proper to the enterprise of clinical research. The roles of clinician and scientist must be integrated to manage conscientiously the ethical complexity, ambiguity, and tensions between the potentially competing loyalties of science and the care of volunteer patients.”

[emphasis added]
Miller, Rozenstein, DeRenzo, JAMA 1998;280:1449-1454

How are the tensions between clinical medicine and research managed?

- Safeguards are provided by “…the presence of an intelligent, informed, conscientious, compassionate, [and] responsible investigator.” Beecher, N Engl J Med 1966;274:1354-1360
- Clinical research is highly-regulated as a result of significant lapses and egregious conduct on the part of researchers.

Is a clinical trial the practice of medicine?

Therapeutic breakthroughs are revolutionary advances in treatment, usually rapidly and dramatically obvious in comparison with historic controls; demonstration of benefit in these cases does not usually require randomized trials. Much more common, however, are new therapies that represent modest, incremental advances over existing treatment and that usually require randomized comparison trials to demonstrate convincingly statistically significant improvement.

Giving voice to the ethical dilemma: research versus clinical care

- The tension between research and clinical care manifests itself in a number of interrelated areas.
- Before we address these, a brief description of clinical trial phases, and of the condition known as equipoise in clinical trials, is in order.

Clinical Trial Phases

- Phase I trials are initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness. They are conducted with either healthy participants and/or patients. They are not intended as therapy.
- Phase II trials are controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks.

Clinical Trial Phases (continued)

- Phase III trials are expanded controlled and uncontrolled studies after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide and adequate basis for physician labeling.
- Phase IV trials are post-marketing studies to delineate additional information including the drug’s risks, benefits, and optimal use.

Equipoise

- A fundamental underpinning of clinical research is the concept of equipoise: sufficient promise for a new intervention but insufficient evidence to justify broad use. (Brody et al. Consensus and controversy in clinical research ethics. JAMA 2005;294:1411-1414)
- In a clinical trial, equipoise translates to indifference in preferring any particular arm of the trial, and a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm.

The tension: an ethical dilemma

The ethical dilemma confronting clinical cancer investigators evaluating potentially useful new agents is not insignificant: While the benefits to science and society of a particular [early stage] trial may be substantial, is it truly justified to treat an individual patient with advanced cancer in such a study when the chances of an objective therapeutic benefit are, on the average, considerably less than 1:20?


How is this tension manifested?

- Phase I trials are explicitly designed to determine the maximum tolerated dose (MTD) in humans.
- Initial human testing of agents that appear promising in pre-clinical studies.
- They are sometimes characterized in discussions with patients as having “therapeutic intent,” playing into a patient’s fear.
- They are the last hope for desperate patients in whom standard therapy has failed.
- Only in Phase II trials do we begin to test efficacy in humans.
How is this tension manifested?

- Washout periods for psychiatric patients:
  
  [The] potential benefits of drug withdrawal protocols include the ability to address patients in a drug-free state and better characterize the nature of the illness, to have baseline assessment to more accurately assess treatment effects, to disentangle behavioral adverse effects of medication from manifestations of the disease...and to identify patients who may sustain remission without medication.

Carpenter, et al. The rationale and ethics of medication-free research in schizophrenia. Arch Gen Psychiatry. 1997;54:401-407

The therapeutic misconception

- First discussed by Applebaum and colleagues in 1982, the therapeutic misconception exists when individuals do not understand that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the participants enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial. (In fact, of course, individuals may actually be harmed by participation in the trial.)

- Overcoming the therapeutic misconception is the primary ethical task of physician researchers.

The therapeutic misconception

- Is a manifestation of the combination of emotion and reason in human decision-making.

- What information means is not solely a function of how it is presented. It also depends on beliefs and emotions.

- In addition, there are both subjective and objective components to the interpretation of medical research.

- It is misleading, therefore, to believe that people make purely cognitive decisions about participation in medical research solely on the basis of medical information presented to them by researchers.


The therapeutic misconception affects everyone

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More on the therapeutic misconception

An investigation of volunteers in four research studies found:

- 69% had no comprehension of the actual basis for their random assignment into a study arm.

- 46% explicitly believed that assignment would be based on therapeutic needs.

- 39% did not understand that their physician would not know the agent they received.

- In two studies with tightly-restricted dosage adjustment rules, 50% thought their dosage would be adjusted according to their individual needs.


A radical proposal

A morally valid consent in research settings requires a radically new personal and professional commitment to the patient-subjects and the informed consent process: Physician-investigators must see themselves as scientists only and not as doctors. In conflating clinical trials and therapy, as well as patients and subjects, as if both were one and the same, physician-investigators unwittingly become double agents with conflicting loyalties.

Some not-so-radical proposals

- There are ethical challenges for the physician researcher between the role of clinician and the role of scientist.
- The ethical tensions between patient care and research requirements must be identified and managed.
- Scientific rigor may need to be sacrificed in order to protect patient volunteers from severe harm or suffering.

Informed consent in clinical medicine – some background

- The term "informed consent" was first introduced in 1957 (Salgo v Stanford University Board of Trustees), although the practice of disclosure of clinical risk has been around for centuries, and a judicial concept since 1767.
- "Reasonable person standard" – whether a patient should be informed of a clinical risk is based on whether a reasonable person in that patient's position would want to be informed. (Canterbury v Spence – 1972)

Informed consent in research

- The informed consent process is the ethical cornerstone of patient-volunteer protections in human research.
- The informed consent document has, over the years, morphed from an explanation of the research process into a highly technical legal document.
- Informed consent is highly regulated, highly visible, and, in my opinion, highly flawed.

Informed consent in research and the Belmont Report

- The Belmont Report recommends the "reasonable volunteer" standard for informed consent.
- The need for volunteers to fully understand to what they are consenting is greater because
  - Research participation is voluntary
  - Alternatives may exist
  - The volunteer may not benefit and may in fact be harmed
- For a clinical trial, federal regulations stipulate eighteen required elements for the informed consent document.

Vulnerable populations – extra protections

- Federal regulations identify five "vulnerable populations" requiring extra protection
  - Pregnant women, fetuses, and neonates*
  - Prisoners*
  - Children*
  - Individuals who are economically or educationally disadvantaged
  - Mentally disabled persons
- KP IRBs also look with extra oversight at KP employees enrolled in studies by virtue of their employment at KP. IRBs can decide that any group is "vulnerable.*

* Protections are codified in the regulations

The over-arching consideration

- The overarching consideration in the informed consent process is risk.
- IRBs tend to focus on things like the readability of the informed consent document.
- What IRBs need to focus on is the communication of risk, and volunteers' understanding of what that risk is – the process, not just the form.
The Matsui paradox

- Matsui et al. evaluated the effect on volunteer understanding of two different approaches to obtaining informed consent:
  - Written materials and an oral explanation (routine approach)
  - Routine approach plus educational lectures and group meetings (intense approach)
- Volunteers in the routine group were more likely to assume that they understood what the research was about


Descriptions of benefits and risks

Analysis of 272 Phase I oncology trial forms found:
- 268 (99%) mentioned that the trial was research
- 269 (99%) mentioned the right to withdraw from the trial
- 260 (96%) referred to the experimental agent as “treatment” or “therapy”
- 14 (5%) mentioned the possibility of a cure
- 255 (94%) communicated uncertainty about benefit
- 11 (4%) said there would be no benefit
- 1 (<1%) form said that subjects were “expected” to benefit


Therapeutic optimism

- The extent to which, on a consent form, therapeutic potential or intent is implied.
- Therapeutic optimism in informed consent forms might make the case that the informed consent is not being guarded against the therapeutic misconception.
- But... consent forms don't capture the discussion between the investigator and the volunteer.


Informed consent versus "informed decision making"

- It has been argued by Kottow that informed decision making exists only in the clinical setting, where the patient is presented with alternative courses of treatment which are standards of care, and can choose the one most compatible with his wishes.
- In the research setting, on the other hand, the participant exercises free will only when deciding to participate in a trial or to opt out. Once in the trial, they must adhere rigorously to its requirements.

Informed consent is imperfect

- In any case, informed consent is an imperfect form of communication between researchers and participants involving more than a value neutral presentation and explanation of medical information.
- It has been argued that informed consent is a value-laden interpretation of information by participants by virtue of their cognitive/emotional state of mind.
- Participants need to recognize that physician researchers are not operating as physicians with their sole concern the best clinical interests of their patients.

Parental permission (de facto consent) in clinical trials

- In pediatric trials, parents are required to consent on behalf of their child. The process assumes that parents are making a rational choice. But...
  - Consent is frequently sought soon after a life-threatening diagnosis, when parents are vulnerable, and highly dependent on clinicians.
  - The volume and complexity of information parents face is new to them, and they don't want to make a "wrong decision."
  - People are motivated to avoid regret by making decisions that minimize its likelihood. This may influence parental decision-making.
Parental permission

- The seriousness of the child’s condition and the urgency surrounding trial entry influence how parents experience trial recruitment, as well as their sense of vulnerability.
- Parents considering oncology trials report high levels of distress during trial discussions and a sense that this impairs their ability to ask questions or request additional information.
- There is also a reluctance to say “no” to the clinical team on which their child’s care depends.
- The possibility of the therapeutic misconception is especially prominent here.

The child’s assent

- It is KP policy in Northern California that unless otherwise stated in the IRB’s approval notification, researchers will obtain and document assent.
  - Children ≤ 6: There is no IRB requirement to obtain assent but the researcher will explain procedures to the child at a level understandable to the child.
  - Children aged 7 – 12: Obtain verbal assent and document in the study notes (child’s study file) or medical record according to site procedures.
  - Children aged 13 – 17: If the IRB approves an age-appropriate assent form or parental permission (consent form) with a signature line for the child to indicate assent, the researcher will obtain the child’s assent, and document the assent by the child’s signature.
- In California, IRBs must approve an assent document for children ≥ 7 years of age.
- When the IRB requires and approves an assent procedure, there is no regulatory provision for researchers or parents/guardians to override a child declining to give assent.

Additional thorny problems with informed consent

- Low socio-economic status (SES) and membership in a minority ethnic group is associated with lower understanding of informed consent.
- Investigators provide less information to ethnic minority parents with low SES, and are less likely to ask their opinion or encourage questions.

How can these problems be addressed? A conundrum

- Parents considering a trial expressed a preference for the trial to be explained to them by regular provider, rather than the principal investigator or research coordinator, suggesting that an already-established clinical relationship provides comfort and familiarity.
- But physicians who have an existing relationship with a family fear that an approach about research might damage that relationship, and investigators may not have confidence in the clinician’s ability to explain the trial.
- Is there a solution?

How to develop professional research integrity

- Appreciation of the differences between clinical medicine and research needs to start in medical school.
- Attention to the ethics of clinical research needs to be paid by senior researchers who train and mentor young researchers.
- Researcher-ethicist collaborations need to be strengthened.

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