What do we owe research subjects?

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When may a physician, consistent with his/her duties, offer the patient enrollment in a clinical trial?

Physician-patient relationship

- Fiduciary relationship:
  - A relationship of inequality in which the fiduciary is granted discretionary power over significant personal interests of the beneficiary
- Duty of care:
  - The physician must act and advise in accord with the patient's best medical interests

Clinical research

- Involves the pursuit of other interests
  - Public interest in knowledge
  - Private interests of industry, institutions, researchers
- Impact of clinical research on patient care
  - To ensure scientifically valid results, the treatment is restricted by design features of the study (randomization, blinding, fixed treatment schedule)
  - Patient-subjects undergo nontherapeutic procedures to answer the study question at hand

Two extremes

- Hellman S, Hellman DS. Of mice but not men. Problems of the randomized clinical trial. *N Engl J Med* 1991; 324: 1585-1589.
  - An unmanageable conflict exists between the interests of the patient-subject and those of others in clinical research
  - RCTs violate the rights of patient-subjects necessarily and unacceptably
  - Abandon RCTs in favor of non-random methods

Two extremes

- Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. *N Engl J Med* 2003; 348: 1383-1386.
  - Clinical research and practice have distinct norms
  - No duty of care in clinical research
  - Physician-researchers are not acting as physicians
  - Physicians-researchers have duties to obtain informed consent and not to exploit patient-subjects

An early solution

- Freedman B. Equipoise and the ethics of clinical research. *NEJM* 1987; 317; 141-145.
  - Clinical equipoise:
  - At the start of a trial there must exist a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment.
  - The trial's treatment arms much each be consistent with competent care.

Questions

1. Where do obligations to research subjects come from?
2. What is the role of REBs?
3. What is the role of the physician-investigator?

Trust

- Trust relationship
  - Relationship of structural inequality in which the more powerful party is granted discretionary power over the significant practical interests of the less powerful party
- The relationship is thus characterized by dependency and vulnerability
- More powerful party has a duty to protect and promote these practical interests

Trust relationships in clinical research

- State and patient-subject
  - Obligation to protect the liberty and welfare interests of patient-subjects generally
  - Regulations/ guidelines
  - REBs act as an arm of the state
- Clinician-researcher and patient-subject
  - Obligation to exercise clinical judgment to protect the medical interests of the individual patient-subject

The State

- Political trust: Relationships in which citizens in democratic states entrust power over public interests to political representatives and public officials
- Clinical research is the source of a critical public good: medical knowledge
- Patient-subjects reasonably expect that the state will protect their interests
- State undertakes obligation to protect patient-subjects and enacts regulatory oversight structures and standards

The REB is an agent of the state and its role is to ensure that the state’s obligations to protect and promote the liberty and welfare interests of the patient-subject are fulfilled.

The State

- What are the welfare interests of patient-subjects?
- As a patient, the patient-subject has an interest in receiving competent medical care
- Obligation to ensure competent medical care
- REB in its review of the study protocol, ensures that therapeutic procedures meet the requirements of clinical equipoise

Clinical equipoise

At the start of a clinical trial, there must exist a state of honest, professional disagreement in the community of expert practitioners as to the preferred treatment.

REB Decision making

- The REB does not survey practitioners.
- The REB
  - scrutinizes the study justification,
  - reviews relevant literature, and,
  - when required, consults with independent clinical experts.
- Clinical equipoise is satisfied if the REB concludes that the evidence supporting the various therapeutic procedures is sufficient that, were it widely known, expert clinicians would disagree as to the preferred treatment.

The State

- As a patient or healthy person, the patient-subject has an interest in not being exposed to undue risk solely for the benefit of others.
- Obligation to protect the patient-subject from undue risks.
- In it review of the study, the REB ensures risks posed by non-therapeutic procedures are
  - Minimized consistent with sound scientific design
  - Reasonable in relation to the knowledge to be gained.

REB Decision making

- An REB ensures that non-therapeutic risks are minimized by, where feasible, requiring the substitution of “procedures already being performed on the subjects for diagnostic and treatment purposes”
- The REB’s determination that the risks of non-therapeutic procedures are reasonable in relation to knowledge requires that it judge the study’s scientific value sufficient to justify risks to subjects
- REB should include community representatives

The State

Referent	Patient	Patient or healthy person
Interest	To receive competent medical care	To not be exposed to undue risk solely for the benefit of third parties
Norm	To ensure competent care	To protect from undue risk
Specification	Therapeutic procedures must fulfill clinical equipoise	Risks of nontherapeutic procedures must: (1) be minimized; (2) be reasonable in relation to knowledge; and (3) if the study population is vulnerable, be no more than minimal risk

Limits of REB review

- REB approval only signifies that a protocol meets general standards mandated by the state
- REB review occurs before any potential patient-subject is approached regarding study participation.
- Physician-researcher retains the obligation to protect the interests of the particular patient-subject

The physician-researcher

- Personal trust: One person entrusts another with specific power over specific personal interests
- Patient-subject cedes to the physician-researcher discretionary power over medical interests
- Creates dependence and vulnerability as the he/she may fail to protect these interests
- Physician-researcher has an obligation to exercise clinical judgment in protecting the medical interests of the patient-subject

Discretionary judgment

- Decision to offer enrollment
  - Eligibility criteria with evaluative terms, e.g., “serious”
  - Patient characteristics or history not covered explicitly by eligibility criteria
- Decision to administer the next protocol procedure
- Decision to withdraw the patient from the study
- In the event of withdrawal, treating the patient-subject

The physician-researcher

- At each decision point in the study, from enrollment, to conduct, to termination, the physician-researcher must exercise judgment
- He/she takes account of the circumstances of the particular research-subject, and acts and advises so as to protect the research-subjects medical interest
- The physician-research acts in accord with the clinical judgment principle

Clinical judgment principle

Knowing that a clinical trial has been approved appropriately by an REB, the physician-researcher may offer trial enrollment (or continuation) unless (1) she believes it would be medically irresponsible to do so, and (2) this belief is supported by evidence that ought to be convincing to colleagues.

Conclusion

- Novel trust-based account of the moral foundation of clinical research
- Clearly articulates roles and responsibilities of the state and physician-researcher
- Specify rules for REB assessment of benefits and harms in research called component analysis
- Clearly identifies as essential the role of clinical judgment in the protection of patient-subjects