Therapeutic Orientation to Clinical Trials

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- The views presented are mine and do not reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

Overview

- Diagnose the “therapeutic orientation” to clinical trials
- Point out ethical problems with the therapeutic orientation
- Respond to objections
- Make recommendations for overcoming the therapeutic orientation

The Development of RCTs

- The randomized controlled trial (RCT) emerged in the mid 20th century
  - "The gold standard" for evaluating treatments.
- RCTs conducted in academic medical centers in context of a close, seamless, connection between research, education, and patient care.

RCTs and Medical Care

- Thomas Chalmers (1981) described the relationship between the clinical trial and routine medical care as follows:
  - "The practice of medicine is in effect the conduct of clinical research . . . Every practicing physician conducts clinical trials daily as he is seeing patients. The research discipline known as the 'clinical trial' is the formalization of this daily process."

The Current Scene

- Within evidence-based medicine the RCT is understood as providing the best evidence for guiding treatment decision-making.
- Increasingly, industry-sponsored RCTs are being conducted by community physicians recruiting their own patients.
- The historical development and the contemporary practice of RCTs promote “the therapeutic orientation” to clinical trials.

Evidence for the Therapeutic Orientation

- In recruitment advertisements, consent documents, and the language reporting the results of RCTs investigators are described as physicians and research subjects as patients.
- It is frequently claimed that the RCT offers patients optimal or “state of the art” medical care.

More Evidence

- “Clinical trials are the ‘practice’ of medicine in the best sense of that term.”
  Lawrence and Bear, Cancer 1995;75:2407-9
- “A clinical trial is just one of many treatment options at M.D. Anderson.”
- Phase I oncology trials are often described as “therapeutic research” or motivated by “therapeutic intent.”

Clinical Setting Reinforces the Therapeutic Orientation

- RCTs conducted in clinical settings.
- Investigators and members of the research team wear white coats.
- Research procedures used to answer scientific questions are performed with the same medical technology used in standard medical care.

The Therapeutic Orientation in Research Ethics

- Declaration of Helsinki, principle #3:
  - "The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration.'"
- Does this belong within a statement of ethical principles governing research with human subjects?

The RCT Dilemma and Clinical Equipoise

- How is it possible for physicians to fulfill their therapeutic obligation to provide optimal medical care when enrolling patients in RCTs?
- Clinical equipoise is invoked to maintain the ethics of the physician-patient relationship within RCTs.

Clinical Equipoise

- RCTs are ethical only if there is uncertainty in the expert medical community about the relative therapeutic value of investigational and control treatments (and the standard of care).
  - Patients should not be randomized to treatments known to be inferior to the standard of care.

Ethical Distinction Between Clinical Trials and Medical Care

- RCTs differ from medical care:
  - Purpose
  - Characteristic methods
  - Justification of risks
  - Relationship between investigators and research subjects

Purpose of RCTs

- To produce generalizable knowledge about treatment efficacy by controlled experimentation in *groups* of patients aimed at promoting improved medical care.
- Contrasts fundamentally with goal of medical therapy to provide personal care for *particular* patients.

Characteristic Methods

- RCTs include randomization, blinding, placebo controls, protocols restricting treatment flexibility, and research procedures to measure study outcomes.
- All of these methods employed to answer scientific questions are foreign to standard medical care.

Justification of Risks

- RCTs include procedures for scientific purposes that carry risks of harm to subjects without a prospect of benefit to them.
  - Justified by anticipated value of knowledge.
- In medical care, the risks of diagnostic procedures and treatments are justified by potential medical benefits to patients.

Ethical Problems with Therapeutic Orientation

- Interferes with realizing informed consent
- Diverts attention from moral tension between scientific investigation and the well-being of research participants
- Provides dubious guidance for design and conduct of RCTs

Informed Consent and the Therapeutic Misconception

- A variety of evidence suggests that many patient-subjects confuse participation in RCTs with medical care.
- If subjects fail to comprehend how RCTs differ from medical care, then they fall short of full informed consent.

The Therapeutic Orientation and the Therapeutic Misconception

- The therapeutic orientation to clinical trials fosters the therapeutic misconception among patient subjects (and also among investigators and ethicists).
- If investigators are not clear about how RCTs differ ethically from medical care, it is unlikely that subjects will understand and appreciate the key differences.

Moral Conflict

- There is an inherent tension within clinical research between pursuing valuable science and protecting and respecting subjects.
- When RCTs are seen as optimal medical therapy, attention is diverted from this moral conflict.
- The therapeutic orientation can promote exploitation and overprotection.

Exploitation

- When investigators recruit and obtain informed consent from their own patients, patients may believe that research participation must be in their best medical interests or that they ought to comply to preserve the relationship.

Flawed Guidance for RCTs

- The therapeutic orientation, guided by clinical equipoise, rules out some valuable placebo-controlled trials that do not pose undue risks to subjects.

- Therapeutic orientation promotes premature stopping of RCTs.

Interim Monitoring

- RCTs often have independent Data Monitoring Committees to review interim data.
- *A priori* statistical guidelines are established to guide decisions on stopping trials early when interim data indicate that treatment A is superior to B on the primary outcome.

Premature Stopping of Trials

- “RCTs stopped early for benefit are becoming more common and show implausibly large treatment effects, particularly those with few events.”
- “A commitment to promptly offer participants in the less favorable group the better treatment choice may motivate investigators, patients and their advocates and the DSMB.” Montori et al. JAMA 2005;294:2203-8.

Equipoise and Stopping Trials

- According to the principle of clinical equipoise it is ethical to conduct an RCT only if “There is no consensus within the expert clinical community about the comparative merits of the alternatives to be tested.” Freedman B. NEJM 1987:317:141-5
  - No participant should receive a treatment known to be inferior.

Equipoise Disturbed

- According to the equipoise doctrine, RCTs should be stopped when equipoise is disturbed.
- Operative rule: RCTs should be stopped when interim data show that treatment A is better than B according to accepted standards of statistical significance.

Problem of Premature Stopping

- When interim data indicate that A is more effective than B, there may be insufficient data to assess the risk-benefit ratio.
- Stopping trials early based on efficacy data may result in widespread use of therapy ultimately found to have an unfavorable risk-benefit ratio.

Letrozole Trial

- Placebo-controlled trial evaluating an aromatase inhibitor as adjuvant therapy for postmenopausal women with breast cancer
- Primary endpoint: disease free survival after 4 years; designed to detect a 2.5% difference
- Trial stopped after median follow-up of 2.4 years
  - Goss et al. NEJM 2003;349:1793-1802

Controversy

- Critics
  - New York Times editorial described early stopping as “ethical overkill.”
  - National Breast Cancer Coalition: not enough known about toxicity
- Defenders
  - “The only ethical option was to unblind the study medication and offer treatment to all participants.” Goss and Ingle, NYT 10/17/03

Letrozole Trial Results

Table 4. Disease-free and Overall Survival in Years 1 through 4.

Variable	Letrozole Group (N=2575)	Placebo Group (N=2582)	Absolute Difference (95% CI)*
	%		
Disease-free survival			
Yr 1	98.6	97.8	0.8 (0.0 to 1.5)
Yr 2	96.7	94.8	1.9 (0.6 to 3.3)
Yr 3	95.2	90.2	5.0 (2.7 to 7.3)
Yr 4	92.8	86.8	6.0 (2.0 to 10.1)
Overall survival			
Yr 1	99.8	99.7	0.1 (–0.2 to 0.4)
Yr 2	98.9	98.6	0.3 (–0.5 to 1.1)
Yr 3	97.7	96.9	0.8 (–0.8 to 2.3)
Yr 4	96.0	93.6	2.4 (–0.9 to 5.6)

* CI denotes confidence interval.

Commentary

- One critic attributed early stopping to “the perceived ethics of depriving study participants of the possibility of a survival advantage . . .”
- “Perhaps we should be more concerned with the possibility of exposing patients (present and future) to potential harm and burdening the medical system with added expense, without fully defining the long-term risks and benefits of a treatment intervention.” Cannistra J Clin Oncology 2004;22:1542-45

Burden of Proof

- The therapeutic orientation places the burden of proof on continuing trials when evidence of superior effectiveness emerges.
- When RCTs are seen as scientific experiments aimed at societal benefit, the burden of proof should be placed on stopping trials early.

Objection to Critique of Therapeutic Orientation

- The therapeutic orientation is necessary to protect subjects from harm and exploitation.
- Without the therapeutic orientation, the rights and well-being of patient-subjects will be sacrificed by pursuit of the social good according to a utilitarian ethic.

Ethical Requirements of Clinical Research

- To protect subjects there is no need to appeal to the ethics of the physician-patient relationship or to therapeutic principles such as equipoise.
- Ethical requirements geared to nature of clinical research provide adequate protection of subjects.

7 Ethical Requirements

- Scientific/Clinical Value
- Scientific Validity
- Fair Subject Selection
- Favorable Risk-Benefit Ratio
- Independent Review
- Informed Consent
- Respect for Enrolled Subjects

Emanuel et al. JAMA 2000;283:2701-11.

Overcoming the Therapeutic Orientation

- Educating investigators, IRBs, clinicians, and patients about ethically significant differences between clinical trials and medical care.
- Reconstructing research ethics to focus on avoiding harm and exploitation and promoting fair terms of cooperation between investigators and research participants.

Overcoming the Therapeutic Orientation

- Careful attention to the language describing clinical trials
  - Recruitment advertisements and consent documents should be scrutinized with an eye to avoid contributing to the therapeutic misconception.

Informed Consent Process

- When the investigator has a prior treating relationship with the prospective subject, someone other than the investigator should obtain informed consent (American Medical Association Council on Ethical and Judicial Affairs).

Morin K et al. Managing conflicts of interest in clinical trials. JAMA 2002;287:78-84.

Conclusion

- Clinical research is a socially valuable but ethically challenging activity, which calls for balancing the pursuit of science and the protection of subjects.
- The ethical conduct of clinical research requires clarity about how clinical trials differ from medical care.