

Comparative Effectiveness Trials and Informed Consent

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Disclaimer

- 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

- Historical introduction
- Examine critically argument for waiving informed consent (IC) in comparative effectiveness randomized controlled trials (CE RCTs)
- Defend simple, verbal consent: integrated consent model

Historical Introduction

- Prior to mid 1960s, RCTs routinely conducted without informed consent
 - Patients received treatment in RCTs under the guise of medical care without being informed about random selection and research

Streptomycin Trial (1947)

- Streptomycin + bed rest vs bed rest alone for tuberculosis
- Patients *not* informed that they were participating in a clinical trial
 - A.B. Hill: “Of course, there were no ethical problems in those days: we did not ask the patient’s permission or anybody’s permission. We did not tell them they were in a trial—we just did it.” Hill AB *Controlled Clinical Trials* 1990; 11:77-9.

Sham Surgery Trial

- Sham controlled trial of internal mammary artery ligation for angina
- “The patients were told only that they were participating in an evaluation of this operation; they were not informed of the double-blind nature of the study.”
 - No mention of randomization or use of sham procedure to evaluate real surgery

Cobb LA et al.. N Engl J Med 1959;260:1115-18.

Advent of Informed Consent

- 1962: Congress directed FDA to require IC for studies of “investigational new drugs”
- 1966: based on research scandals, NIH mandated IC to clinical research and oversight by Institutional Review Boards (IRBs)
- IC with detailed written consent documents became standard practice for RCTs

Regulatory Consent

- Elements of IC
 - Study involves research; description of research procedures
 - Reasonably foreseeable risks/discomforts
 - Anticipated benefits to subjects
 - Alternatives
 - Protection of confidentiality
 - Whom to contact to answer questions
 - Participation voluntary, no penalty for refusal or dropping out

45CFR46.116

Comparative Effectiveness Research

- Most new drugs approved by FDA on basis of placebo-controlled trials, with narrowly defined patient eligibility criteria
- Limited rigorous data to support choice between approved drugs in routine practice
- Growing interest in CE RCTs to close gap in evidence for sake of improved patient care

Institutional Promotion of CER RCTs

- NIH Collaboratory (2006)
 - Supports “the design and rapid execution of several high-impact pragmatic clinical trial demonstration projects.”
- Patient-Centered Outcomes Research Institute
 - Established 2010 under Affordable Care Act
 - Mandate: “improve the quality and relevance of evidence available . . . to make informed health decisions.”
 - Funds CER projects

Burden of IC

- Detailed IC in accordance with required elements arguably impedes performance of needed CE RCTs
- Reluctance of physicians to disclose randomization and patient refusal of IC can introduce selection bias
 - Outcomes of studies may not reflect population of patients in routine practice

Options for CE RCTs

- “regulatory consent”: detailed written consent conforming to federal regulations
- Waiving consent to research (with IRB approval)
- Simple, verbal consent integrated with consent to treatment

Waiving IC for some RCTs?

- Truog et al: “Is informed consent always necessary for randomized controlled trials?”
- Waiving IC should be permitted when treatments being compared are medically indicated and have similar risk-benefit profiles

Truog RD et al. N Engl J Med 1999; 340:804-6.

Example

- RCT of 2 antibiotics to prevent infection after surgery
 - Treatment A: older, generic drug
 - Treatment B: newer, on-patent drug
 - A and B never compared head-to-head
- IC can be waived provided IRB judges that “no reasonable person should have a preference for one treatment over the other.”

Contemporary Debate

- Argument by Truog et al: shot in dark, little traction in bioethics
- Recently, renewed interest in waiving IC for some CE RCTs in context of “learning health care system” (LHCS).

LHCS

- Model of LHCS: seamlessly integrate clinical research and medical care via use of data routinely entered into electronic medical records
 - Observational studies (e.g., quality improvement interventions, treatment side effects)
 - Pragmatic CE RCTs
 - QI interventions
 - Individual treatments

Faden et al

- RCTs of 2 approved drugs for a condition: e.g., antihypertensive agents
 - Computer selects treatment A or B
 - Physicians can override based on clinical judgment
 - No additional risks or burdens for patients
 - Prior notice that such studies will be conducted within LHCS
 - Patients consent for treatment but not research

Faden R et al. Medical Care 2013;51: S53-S57.

Rationale for Waiving IC

- On current evidence, no welfare interests of patients compromised in randomizing patients to drug A and B
 - “Patients interests in exercising personal preferences, and the role clinicians have in advocating for those preferences, are limited” (S56)
- Are welfare interests the only ethical considerations relevant to soliciting consent to treatment research?

IC and Respect for Persons

- Argument: waiving IC for treatment RCTs violates respect for persons
- Respect: vague and capacious norm
 - Need to unpack and specify respect for context of receiving medical care in RCTs
 - Useful source of guidance in Charles Fried's (1974) account of "the system of rights in personal care" in *Medical Experimentation*

Fried

- First systematic account of ethics of RCTs
- Major concern with practice of conducting RCTs in guise of medical care w/o IC
 - “Specifically in the case of the RCT must the doctor disclose the fact that the patient’s therapy will be determined by a randomizing procedure rather than an individualized judgment on the part of the physician?” (32)

Personal Care

- Package of legitimate expectations (rights) of patients and obligations of clinicians with respect to medical care
- 4 components
 - Lucidity (transparency)
 - Autonomy
 - Fidelity
 - Humanity

Transparency

- Obligation of physicians to inform patients about relevant facts concerning their medical condition and discuss recommended treatment plan
- Informing component of IC

Autonomy

- Patient given opportunity to decide whether or not to accept doctor's recommended treatment plan
- Making treatment plan consistent with patient's preferences and values emerges out of transparent communication and opportunity to authorize plan

Fidelity

- Doctor's orientation to promoting medical best interest of individual patient and patient's legitimate expectation that recommended treatment will be guided by this orientation
- Fidelity underwrites trustworthiness of doctor and patient's trust

Humanity

- Responsibility of clinicians to care for and care about particular patients
 - In contexts such as medical care, “a person has a right to have his full human particularity taken into account by those who enter into relations to him” (103).

Application to CE RCTs

- Fried sees RCTs w/o IC as form of “deceit,” violating legitimate expectations to personal care
 - Lack of transparency about treatment selection
 - No opportunity to authorize departure from standard medical care and research participation
 - Contrary to expectation of doctor’s individualized judgment in recommending treatments

Objection

- Doctors not expected to explain their reasons for recommending approved drug A vs B when no evidence about comparative effectiveness
 - Treatment selection essentially “random”
- Why, then, should they be obliged to disclose formal randomization in CE RCTs?

Reply

- RCT alters relationship between doctor and patient with implications for personal care
 - Effort to answer scientific question via RCT governs treatment selection
 - Randomization not oriented to medical best interests of individual patients, even though not necessarily contrary to fidelity
 - Legitimate expectations of patients to personal care deceptively infringed absent IC

What is at Stake?

- Major ethical concern not merits of selecting drug A or B—not a matter of welfare
- Rather, concern for respect of patient as person
 - Transparency of relationship between doctor and patient
 - Patient's opportunity to authorize departure from personal care by opting to enroll in RCT

Prior Notice

- Does prior notice that treatment sometimes will be selected in LHCS via RCTs obviate ethical concerns about lack of IC?
 - Reasons to be concerned about meaningfulness of “boilerplate” disclosures
 - Patients left in the dark about whether their treatment in any given instance recommended based on doctor’s judgment or determined by RCT

Integrated Consent Model

- False dichotomy of regulatory consent or waiver of consent
- Simple verbal disclosure integrating consent for treatment and research
 - Reasons for RCT, fact of randomization, and opportunity to authorize (opt-in or opt-out)
- Consistent with “alteration” of IC in federal regulations

Kim S, Miller FG. N Engl J Med 2014; 370:769-72.

Waiver/Alteration Requirements

- (1) the research involves no more than minimal risk to the subjects;
- (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) the research could not practicably be carried out without the waiver or alteration; and
- (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.”

45 CFR46.116(d)

Comparing Models

- No consent
 - Adversely affects rights (personal care)
 - Research with some IC process is practicable
- Integrated consent
 - Does not adversely affect rights: qualifies as valid consent
 - Regulatory consent would not be practicable for many pragmatic CE RCTs

Scientific Penalty

- Whenever IC required, opens door to selection bias: some % of patients will refuse
- Empirical question whether CE RCTs with integrated consent will introduce substantial selection bias vs those w/o IC
- Tolerating some selection bias is ethical price we need to pay out of respect for persons

Quality Improvement RCTs

- Truog et al mentioned RCT of 2 brands of disinfectant soap for use by clinicians to prevent hospital-acquired infections
- This type of RCT importantly different from CE RCTs of individual treatments

QI RCTs

- Hospitals have discretion to select routine operating procedures applying to all patients: e.g. selection of soap, staffing patterns in units
 - Patients not informed or consulted
- RCTs of hospital procedures consistent with standard of care justifiable w/o IC
- No legitimate expectations relating to personal care at stake

Conclusions

- We should encourage CE RCTs in LHCS
- Waiving IC neither necessary nor desirable in RCTs of individual treatments
- Empirical research on attitudes of public and patients can help guide thinking about the type of consent that is consistent with respect for persons