Module 3: R

Ethics

Data Sciences Institute, University of Toronto

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Overview

Consent in research design

Case Study: ECMO and randomized trials

- James H. Ware, 1989, ‘Investigating Therapies of Potentially Great Benefit: ECMO’, Statistical Science.
- Donald A. Berry, 1989, ‘Comment: Ethics and ECMO’, Statistical Science.

Consent in research design

Voluntary consent

The voluntary consent of the human subject is absolutely essential. This means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. This latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.

The Nuremberg Code (1947)

Case Study: ECMO and randomized trials

Randomized consent

- Proposed by Zelen (1979)
- Only patients assigned to the non-standard treatment are approached for consent
- Avoids asking people in stressful situations to consent to a treatment that they don't end up receiving

Adaptive randomization

- Based on randomized urn designs (Wei and Durham, 1978)
- Bartlett et al. (1985) assigned treatments sequentially, with the outcome of each treatment affecting the probabilities of the next selection. If a subject was assigned treatment A and survived, the probability of selecting treatment A for the next subject was increased; if the subject died, the probability of selecting treatment B was increased. The study ended at a set number of participants.

Equipoise

- Uncertainty about which of two treatment is superior (Freedman, 1987)
- If evidence is accumulating for the superiority of one treatment, further randomization of treatment becomes ethically concerning

Ware's study design

- Patients are initially assigned randomly to two treatments. When a set number of deaths occur in treatment group A, all subsequent patients are assigned to the treatment B until the set number of deaths occurs in treatment group B, or until the number of survivors establishes the superiority of treatment B.
- Infants were assigned by randomized permuted blocks designs to the established treatment (CMT) and the newer treatment (ECMO). Randomization ceased when four patients died in one treatment arm.

Study outcomes

TABLE 1

Survival experience of patients randomized to ECMO and conventional therapy (CMT) during phase 1, the randomized phase of the trial, and phase 2, the nonrandomized phase

	Phase 1		Phase 2	
	ECMO	CMT	ECMO	CMT
Lived	9	6	19	0
Died	0	4	1	0

Berry's critique

Consent and informedness

Ware strived "To balance ethical and scientific concerns...." There should be no compromise here: Ethical concerns win.

Berry's critique

Equipoise

In my view, the Ware study should not have been conducted. Randomizing patients to conventional therapy in the face of substantial evidence concerning the superiority of ECMO seems unethical.

Discussion questions

What ethical issues do you see with randomized consent?

At what point do we consider equipoise to be void?

Should randomization have continued throughout the study rather than ceasing at a certain point?