Ethical issues in cluster randomized trials

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Indications for a cluster design

• When the intervention operates at the community, rather than (or as well as) the individual, level
• When the intervention is applied to the care-giver, rather than directly to the patient
• When it is easier or cheaper to randomize clusters
• When there is a risk of contamination
• When there is likely to be a ‘therapist’ effect (indicates a clustered analysis)
Potential drawbacks of CRTs

- Sample size inflation
- Two-stage recruitment (cluster and individual)
- Threats to internal validity:
  - contamination;
  - selection bias;
  - confounding by centre
- Statistical analysis is more complex
- Possible lack of credibility of findings from CRTs

Categories of CRTs

Cluster-cluster versus individual-cluster (Edwards et al, 1999)

*essentially equivalent to*

Type A versus Type B (MRC, 2002)
Specific ethical requirements (e.g. informed consent, confidentiality, avoidance of harm) should be fulfilled, unless they are partially or fully overridden by other morally-relevant considerations.

Few, if any, ethical requirements are absolute.

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1. Is the CRT design *per se* ethically justifiable?
2. Is the CRT design compatible with the notion of equipoise?
3. To what extent is consent achievable within a CRT?
'CRTs should be avoided unless individually randomised trials are scientifically inferior or practically impossible. Investigators should justify why they cannot use an individually randomised design and explain carefully why a CRT is preferable'. (MRC, 2002)

The RCT is in principle more resistant to the drawbacks affecting the CRT – a more 'robust' design

How can the CRT therefore be justified?
Performing a CRT versus performing an RCT

or

Performing a CRT versus not asking the question

Question to consider 1

Is a CRT the most methodologically appropriate design for the research question?
The principle which states that, at the outset of a clinical trial, there should be genuine uncertainty in the mind of the researcher as to whether the one or the other treatment is therapeutically superior.

Any clinical preference for one or other treatment must be as yet unsubstantiated.

**Equipoise**

"In general terms, do I have a reason to prefer Treatment A over Treatment B?" – a decision on taking part in the trial

“Do I have a reason to believe, a priori, that Treatment A will be better than Treatment B for this patient?” – a decision on recruiting this patient to the trial

**Elements of equipoise**
Equipoise in the CRT

Equipoise is normally interpreted in terms of the (non)optimality of the intervention for the individual.

This is not possible when the intervention is at cluster level; equipoise may have to be interpreted in terms of the ‘average’ patient.

In an individual-cluster trial, there may be no available alternative intervention.

Question to consider 2

Can the demands of equipoise be fulfilled within a CRT design?
**Informed consent**

The voluntary and revocable agreement of an individual to participate in a study, based on an adequate understanding of the nature of the study and the likely consequences of taking part.

Based on the idea of respect for autonomy.

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**Consent to what?**

1. Consent to the trial occurring
2. Consent to a particular intervention within the trial
**Consent: cluster-cluster CRTs**

Individual consent is not really feasible, as there is little scope for opt-out from either the trial or the treatment

*but*

Individual consent might not normally be expected for this type of intervention

*The difficulty of individual consent is counterbalanced by a lack of need for such consent*

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**Consent: individual-cluster CRTs**

Individual patients cannot consent to the trial, but can choose to consent or not to consent to the treatment

*but*

Alternatives to the intervention being tested may be unavailable or logistically problematic

Consent from controls may induce contamination

Special problems with non-competent members of a cluster

*Individual consent to treatment is possible, but may be inert or give rise to methodological difficulties*
Alternatives to consent

- No consent (or presumed) consent
- Informing that the study is happening (or that it has happened)
- ‘Consent’ via a guardian (Edwards et al, 1999) or ‘cluster representation mechanism’ (MRC, 2002)
- Only consent the treatment arm (à la Zelen)
- Rely on other ethical safeguards

Question to consider 3

Can the demands of autonomy be fulfilled within a CRT design?
References


