Ethics in cluster randomized trials

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Why do CRTs pose ethical issues?
1. CRTs involve groups rather than individuals

**Individual randomized controlled trials:**

- Involve individuals, commonly patients
- Ethics are well understood and aim to protect the liberty and welfare of individuals

**Cluster randomized controlled trials:**

- Involve social groups, the moral status of which is not well understood
- Group interests may conflict with individual interests, complicates benefit-harm assessment
2. The units of randomization, intervention, and outcome assessment differ within any given trial

Individual randomized controlled trials:

- Units of randomization, intervention and outcome assessment are the same

Cluster randomized controlled trials:

- Complex and have multiple levels
- Complicates the identification of research participants
- From whom is informed consent required?
3. Clusters may be randomized before cluster members can be approached for informed consent

Individual randomized controlled trials:

- Patients are identified and approached for consent prior to study participation

Cluster randomized controlled trials:

- Clusters may be randomized prior to identification of individual cluster members
- Is consent to randomization required?
- May gatekeepers provide consent to randomization?
4. **Intervention may be directed at the level of the individual or the level of the cluster**

**Individual randomized controlled trials:**
- Study interventions are directed at the patient

**Cluster randomized controlled trials:**
- Study interventions may be directed at the individual or the cluster, or both
- Cluster-level interventions may be difficult for cluster members to avoid
- Refusal of study participation may be meaningless
The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

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Introduction

Cluster randomized trials (CRTs), also known as group randomized, place-based, or community intervention trials, are systematically explored. As a result, researchers and research ethics committees (RECs) currently lack specific guidelines to help them design, conduct, and review CRTs according to internationally accepted ethical standards. Predictably, the lack of
Ottawa Statement (2012)

1. Justifying the cluster randomized design
2. REC review
3. Identifying research participants
4. Obtaining informed consent
5. Gatekeepers
6. Assessing benefits and harms
7. Protecting vulnerable participants
Who is the research participant?
Research participants

- The units of randomization, intervention, and outcome assessment differ within any given trial.
- Identification of research participants is logically prior to the application of protections.

Two errors:
- Over-inclusive definition runs the risk of unduly burdening research.
- Under-inclusive definition will fail to provide protections to those who have a right to them.
Research participants

• An individual whose interests may be affected by study interventions or data collection procedures

• A research participant is an individual…
  1. Who is the intended recipient of an experimental (or control) intervention; or
  2. Who is the direct target of an experimental (or control) manipulation of his/her environment; or
  3. With whom an investigator interacts for the purpose of collecting data about that individual; or
  4. About whom an investigator obtains identifiable private information for the purpose of collecting data about that individual.
Research participants

- In public health studies in which an entire community is intervened upon, all community members may be research participants.

- In knowledge translation studies, health professionals who are intervened upon are research participants.

- Patients of those health professionals are not research participants unless they are otherwise intervened upon, interacted with, or their private health information is collected.
Research participants

Devon Active Villages Evaluation trial (cluster-cluster)
• Residents of villages (2+3)

Computerized guidelines for asthma/ angina (professional-cluster)
• Physicians (1)
• Patients (3+4)

Cleansing of the umbilical stump (individual-cluster)
• Mothers (3) and neonates (1)
Who must provide informed consent?
Informed consent

- “Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a REC under specific circumstances.”
- Heuristic: “Get consent where you can.”
Informed consent

- Health providers commonly research participants in CRTs
  - Knowledge translation interventions
  - Health services interventions
- Researchers and RECs may fail to recognize health providers as research participants
- Health professionals are entitled to the protection of REC review and informed consent (unless a waiver applies).
Informed consent

- Waiving the consent requirement can only be justified when it is necessary to do so, and when the risk involved is minimal.

- According to the *Ottawa Statement* a waiver of consent may be appropriate when participation poses only minimal risk and:
  - Cluster-level intervention is difficult or impossible to avoid; or,
  - Due to cluster size or other factors, requiring informed consent makes the study infeasible.
Informed consent

Devon Active Villages Evaluation trial (cluster-cluster)
- Waiver of informed consent for study intervention
- Consent for postal survey

Computerized guidelines for asthma/angina (professional-cluster)
- Informed consent is required from physicians
- Waiver of consent for patient records; consent for postal survey

Cleansing of the umbilical stump (individual-cluster)
- Informed consent from mothers.
What is the role of gatekeepers?
Gatekeepers

- “[A]n individual, body, or mechanism that can represent the interests of the cluster”

- Gatekeepers do not have the authority to provide proxy consent on behalf of cluster members, and CRTs should not proceed on the basis of such “consent”.
Gatekeepers

• When a CRT may substantially affect cluster or organizational interests, gatekeepers may protect group interests

• Consultation with cluster members may protect group interests by subjecting the study to examination and discussion by those whose interests may be affected

• Permission is appropriately sought when a gatekeeper has the legitimate political authority to provide it; for example:
  • School principal may provide permission after considering staff availability, financial implications, and teachers/students willingness
Gatekeepers

Devon Active Villages Evaluation trial (cluster-cluster)
- Community consultation and permission

Computerized guidelines for asthma/ angina (professional-cluster)
- Permission of practice manager

Cleansing of the umbilical stump (individual-cluster)
- Permission of public health/ community development authority.
Ethics and Pragmatic RCTs Research Group