Ethical issues in cluster randomised trials in health research

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Ethics and CRT design

- Cluster randomised trials pose difficult ethical issues because of features of their design

1. CRTs involve groups rather than individuals
2. The units of randomisation, experimentation, and observation differ within any given trial
3. Clusters may be randomised before cluster members may be approached for informed consent
4. Intervention may be directed at the level of the individual or the level of the cluster

Bed nets to prevent malaria

- **Unit of randomisation**: Cambodian communities
- **Intervention**: Bed nets distributed to all residents in the intervention communities
- **Data collection**: Population size was obtained from local census data and the number exposed to malaria was obtained from blood tests performed on a random sample of village residents. No identifying information on sampled individuals was retained
- **Result**: Non-significant trends toward decreased malaria incidence.
    - Sochantha T, Hewitt S, Nguon C, et. al.: Insecticide-treated bednets for the prevention of Plasmodium falciparum malaria in Cambodia: a cluster-randomized trial. *Trop Med Int Health* 2006; 11(8): 1166-77.

COMMIT Trial

- **Unit of randomisation:** US and Canadian Communities
- **Intervention:** Multimodal community-level intervention to reduce cigarette consumption including media and billboard campaign and targeted messaging toward smokers from health professionals
- **Data collection:** Interviews with a random sample of smokers in each community, the amounts of tobacco purchased by people living in the intervention and control communities.
- **Result:** Intervention led to an improved quit rate for mild to moderate smokers, with no effect on the quit rate of heavy smokers.
    - The COMMIT Group. Community intervention trial for smoking cessation (COMMIT): II. Changes in adult cigarette smoking prevalence. *Am J Public Health* 1995; 85(2): 193-200.

Improving primary care prescribing

- **Unit of randomisation:** General practitioners in Ireland
- **Interventions**: Personalized summary by mail of prescribing practices of antiplatelet and lipid lowering drugs plus an educational visit versus personalized summary of prescribing practices alone
- **Data collection**: Data on prescribing practices from the national pharmacy insurance program database. Data on prescribing practices were aggregated by physician and contained no identifiable information.
- **Result**: Both interventions led to similar improvements.
    - Naughton C, Feely J, Bennett K: A Clustered Randomized Trial of the Effects of Feedback Using Academic Detailing Compared to Postal Bulletin on Prescribing of Preventive Cardiovascular Therapy. *Fam Pract* 2007; 24: 475-480.

Lack of ethical guidance

- As a result of design features, CRTs pose challenges to our current understanding of research ethics
- Researchers currently lack authoritative guidance to aid design and conduct cluster trials according to the highest ethical standards
- Research ethics committees and regulators have no single international standard to guide their review of cluster trials
- Predictably, the lack of authoritative guidance has resulted in uncertainty and markedly different interpretations as to permissible practices in cluster trials.

Trials

BioMed Central

Study protocol

Open Access

Ethical and policy issues in cluster randomized trials: rationale and design of a mixed methods research study

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Objectives

1. To identify ethical issues arising in the design, review, and conduct of CRTs:
   - Interviews with experienced cluster trialists and methodologists;
   - Review of ethical issues reported in cluster trials;
   - Web based survey of cluster trialists;
   - Web based survey of research ethics committee chairs; and,
   - Focus groups with cluster trial participants
2. To analyze ethical issues in CRTs systematically;
3. To develop guidelines for the ethical conduct and review of CRTs through an international consensus process meeting in Ottawa on November 28-30, 2011.

Ethical analysis

1. Who is the human research subject?
2. From whom, how, and when must informed consent be obtained?
3. Does clinical equipoise apply to CRTs?
4. How do we determine if the benefits outweigh the risks of CRTs?
5. How ought vulnerable groups be protected in CRTs?
6. Who are gatekeepers and what are their responsibilities?
   - *Trials* 2011; 12: 100.

Who is the human research subject in CRTs in health research?

Trials 2011; 12: 183.

A prerequisite for ethics protections

- The identification of human research subjects is logically prior to the application of protections
- For instance, the ethical and regulatory requirement to obtain informed consent only applies to human research subjects
- Two errors:
  - Over-inclusive definition runs the risk of unduly burdening research
  - Under-inclusive definition with fail to provide protections to those who have a right to them

Definition and criteria

- Definition: An individual whose interests may be compromised as a result of interventions in a research study
- A human research subject is…
  1. An individual directly intervened upon by a researcher;
  2. An individual who is deliberately intervened upon via manipulation of his/her environment;
  3. An individual with whom a researcher interacts to collect data; or,
  4. An individual about whom an investigator obtains identifiable private information.

Who is a human research subject?

Example 1: Bed nets to prevent malaria

- Residents of intervention communities who received bed nets or who gave blood samples (1)
- Residents of control communities who gave blood samples (1)

Example 2: COMMIT Trial

- Residents of intervention communities (2+3)
- Residents of control communities who were interviewed (3)

Example 3: Improving primary care prescribing

- Physicians (all were intervened upon) (1)
- Not their patients (no interventions; no private information)

When is informed consent required in CRTs in health research?

Paper under review.

Challenges to informed consent

- Cluster level interventions
  - It may be difficult to avoid the intervention, making refusal of informed consent meaningless
  - With very large clusters, requiring informed consent may make the study infeasible
- Clusters may be randomised before cluster members can be approached for informed consent.

Moral purpose of informed consent

- Moral imperative to treat people not as mere means to an end, but as ends in themselves
- Thus, I may legitimately involve other people in my project, only when they adopt the ends of my project as their own
- *The function of informed consent is to allow prospective research subjects to adopt the ends of the study as their own, thereby (partially) justifying exposing subjects to risk for the benefit of others*
- Not obtaining informed consent requires justification; otherwise the study cannot proceed.

Waiver of informed consent

- When people are not human research subjects, their informed consent is not required.
- Waiving the consent requirement can only be justified when it is necessary to do so, and when the risk involved is insignificant
- Waiver of consent requires:
  - Research involves no more than minimal risk; and
  - Requiring informed consent would make the study impracticable. (Often the case for cluster level interventions).

Post-randomisation consent

- Often in CRTs clusters are randomised before cluster members can be approached for consent
- So long as informed consent is sought as soon as possible and before any study interventions or data collection procedures, consent to randomisation per se is not required
- The moral ends of informed consent can be fulfilled fully
- The content of the informed consent may be tailored to the study arm to which the person's cluster has been randomised. There may be no need to provide a detailed account of study procedures in other trial arms.

When is informed consent required?

Example 1: Bed nets to prevent malaria

- Waiver of consent for bed net distribution
- Informed consent is required from those who give blood
- No consent to randomisation is required.

Example 2: COMMIT Trial

- Waiver of informed consent
- No consent to randomisation

Example 3: Improving primary care prescribing

- Informed consent is required from physicians
- Patients are not human research subjects and no consent is required.

What is the role and authority of gatekeepers in CRTS in health research?

Paper in preparation.

Gatekeepers

- Gatekeepers are unique to CRTs
- UK MRC *Cluster Randomised Trials: Methodological and Ethical Considerations:* "Agreement to participation in the trial will normally be necessary from one or a series of gatekeepers...an individual, body, or mechanism that can represent the interests of the cluster"
- The use of gatekeepers stems primarily from difficulties in obtaining individual informed consent when individuals are approached after cluster randomization, or when a when the intervention is delivered at the level of the cluster

Protecting individual interests

- The emphasis in the CRT literature is the protection of individual interests
- Gatekeepers have given:
  - Permission to randomise
  - Consent for individuals
  - Permission to approach prospective research subjects
  - Information that identifies cluster members

Protecting individual interests

- It is difficult to see how the gatekeeper might reasonably be thought to have the authority to act as a surrogate decision maker
- Gatekeepers usually have neither a close personal relationship with cluster members nor a detailed knowledge of their wishes, values, or interests
- When the gatekeeper is a physician or teacher, the gatekeeper might usefully protect the interests of a cluster member by giving permission to approach.

Protecting cluster interests

- Gatekeepers play a role in protecting the interests of the cluster, at least in certain cases
- Gatekeepers have give:
  - Cluster consent
  - Cluster consultation
  - Protocol approval

Protecting cluster interests

- Cluster consent is only appropriately sought from a legitimate political authority empowered to make binding decisions on behalf of cluster members
- Cluster consultation may usefully address cultural or community concerns in research implementation and may be sought when cluster has a common history, common culture, and other characteristics that provide cohesiveness to the group
- May be a role for protocol approval, especially when research takes place in developing countries.

Protecting institutional interests

- Gatekeeper permission is commonly sought from institutional administrators, including school principals, hospital CEOs, or nursing home directors
- Such permission is conceptualized as permission on behalf of cluster members or the cluster as a whole
- “The ethical principle here is that the [gatekeeper] must act in good faith, and in this regard only in the interests of the cluster represented…[Gatekeepers] CRMs should be independent of the research team, and careful to avoid conflicts of interest.” (MRC 2002)

Protecting institutional interests

- When CRTs are situated in hospitals, nursing homes, or schools, there are legitimate institutional interests at stake
- Requires gatekeepers to determine what impact a research partnership will have on an organization and whether it has the available resources to allow participation
- This decision will be based on availability of staff, the financial implications of participation, and other factors.

What is the role and authority of gatekeepers?

Example 1: Bed nets to prevent malaria

- Community consultation and consent

Example 2: COMMIT Trial

- Community consultation and consent

Example 3: Improving primary care prescribing

- None.

Consultation process

http://crtethics.wikispaces.com/

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Trials – http://www.trialsjournal.com/

CRT wiki site – http://crtethics.wikispaces.com/