SELECTED SUMMARY

Ethics in cluster randomised trials: a grey zone

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Weijer C, Grimshaw JM, Taljaard M, Binik A, Boruch R, Brehaut JC, Donner A, Eccles MP, Gallo A, McRae AD, Saginur R, Zwarenstein M. Ethical issues posed by cluster randomised trials in health research. *Trials*. 2011 Apr 20;12:100.

Cluster randomised trials (CRTs) are controlled trials in which the randomisation is applied to groups of individuals (clusters) as opposed to individual research participants. CRTs are increasingly being used in a wide variety of research with public health implications (including education). Well conducted CRTs can have a significant effect on policy-making. However, CRTs are only justified in specific circumstances where they might be considered suitable: this might be for reasons of scientific validity, feasibility, appropriateness, to reduce chances of contamination, etc.

The authors of this article have focused on the ethical issues which arise while using CRT interventions in health research (1). The article draws from a project funded by the Canadian Institutes of Health Research (CIHR) aiming to work towards the development of international guidelines in this area.

The need to examine the ethics of CRTs

The authors highlight the fact that there is a lack of guidance for investigators, regulators, as well as research ethics committees, on how to examine the ethical challenges which might arise in CRTs. This has led to a lack of standardisation of approaches and differences of opinion about how CRTs should be conducted and regulated. Part of the problem arises because conventional research ethics examination of randomised clinical trials focuses on the individual as the unit of randomisation; linked to this is the requirement for autonomous decision-making of the participant and welfare interests focused on minimising risks.

The authors surmise that currently there is, broadly, a convergence of the principles applicable in research ethics: respect for persons (leads to requirements around informed consent and confidentiality), beneficence (risk-benefit analysis), justice and respect for communities.

CRTs, according to the authors, are challenging because: (a) they involve groups and not individuals -- and the moral status of groups is unclear -- and there is no common understanding on the same; and (b) unlike usual randomised control trials where the individual is the focal unit, the units of randomisation, experimentation and observation might differ in a CRT.

Given this dissonance, the authors present six areas in which they feel it is crucial for a CRT to be ethically sound.

Who is the research subject?

Ethics guidelines offer protection to research participants (subjects). The challenge in CRTs might lie in identifying who the subject in an intervention is. For example, in a CRT the intervention might be applied to healthcare providers while the outcomes are measured on patients. Alternatively, the intervention is applied at the level of the community while the data are collected only on small subgroups within the community.

From whom, how and when should the informed consent be obtained?

Often in a cluster-level intervention, individual consent might be considered meaningless because even if an individual refuses to consent, he/she might still be exposed to the study intervention being applied at the whole cluster level. Also, if the intervention does not directly affect certain individuals, the individuals concerned might not be considered research subjects -- and hence there might be no need for informed consent. Additionally, the usual conditions for consent waiver might be applicable in the study.

However, if the intervention is being applied at an individual level, then the regular expectations and requirements of consent would be considered appropriate. This might however be complicated in behavioural interventions where the consent process at the individual level might lead to treatment contamination (the knowledge of the intervention might lead the individuals in the control group to adopt the intervention as well).

The timing of the consent can also be an area of dispute: whether it should be prior to or after randomisation.

CRTs and clinical equipoise

Concerns are often raised about the fact that those in the control arm in a cluster trial do not receive any benefits of trial participation, and are often burdened with requirements of data collection. Some researchers choose to offer nominal benefits, or choose to delay the benefits related to intervention

in the control arm. This does not however address the concerns raised about the control arm being neglected in the provision of benefits of the intervention.

Since data safety monitoring boards are usually not engaged for CRTs, these trials might not be stopped early based on strong evidence of harm or considerable benefit in one of the arms.

Additionally, the classic requirements of clinical equipoise in a research study might best apply to usual trials involving physician-researchers and patient-subjects, and the authors feel that it might be challenging to use the concept of equipoise in the case of CRTs. They have since published a paper on this specific issue of clinical equipoise in CRTs (2).

Evaluating a positive benefit to risk ratio

Examining the risk and benefit components of CRTs can face hurdles, especially in those trials which involve public health interventions (often with complex components). The authors point out that there might be a difficulty in classifying the interventions as therapeutic or non-therapeutic. Further, extrapolating the concept of minimal risk from the level of individuals to clusters would require more deliberation.

Protecting vulnerable groups in CRTs

Justice requirements include the need to have mechanisms for enhanced protection of vulnerable groups. However, this can pose a challenge either when CRTs are being conducted on vulnerable populations, or when vulnerable populations are a part of the clusters under study. The requirements of standard of care, mired in its own global vs local debate, in the control arm can also be a ground for discord. Linked to this is the issue of post-trial access: for how long and by whom?

Identifying gatekeepers and their responsibilities

The authors highlight how the increasing focus on community engagement in health research has led to approaches which support the need for exploring community consent in addition to individual consent. Community consent might work in certain CRTs which are focused on randomising communities, but might not be relevant in others. Linked to respecting the rights of communities has been the utilisation of gatekeepers to help in developing a respectful community-investigator relationship. The authors state that gatekeepers can most easily be identified in contexts with clear political and administrative delineations, but this might not be the case in many CRTs. The possibility that the gatekeepers may have a conflict of interest that leads to their compromising their role in protecting community interests also needs to be considered; additionally, community interests might not always be synergistic with the institutional or individual interests of the gatekeepers.

Discussion and learning for the Indian context

The paper serves as an interesting introduction to the ethical concerns around CRTs. As this is part of a series of papers, the authors do not delve in depth into the issues they highlight as being problematic, and instead refer the readers to upcoming publications in the series. Fortunately, the series is being published in an open-access journal. The authors are also engaging the wider academic community in discussing their findings through a wiki-site (http://crtethics.wikispaces.com/).

The use of examples from a variety of disciplines helps the reader visualise the concerns the authors raise from a practical perspective. Since the aim of the authors is to scan the area comprehensively and involve various stakeholders with the aim of developing specific guidance in the ethics of CRTs, the article series and other outputs from the project can serve as an important resource. However, developing guidelines and publishing is not enough, and efforts will need to be made to evaluate the applicability of the findings from the papers in all contexts; the key concepts must be integrated in public health and investigator training programmes.

Some of the findings of Weijer and colleagues have also been mirrored by researchers who have experience in conducting health CRTs in Asia and Africa (3). In India, specifically, concerns around the use of cluster trials and ethical implications have been raised. Examples include the Gadchiroli home-based neonatal care trial, which though not involving randomisation of clusters has been the subject of critical examination in this journal for the last few issues. Concerns have also been raised about the Narangwal study. In both these studies, most of the debate focuses on the obligation of researchers towards the individuals and communities within the control clusters. The possibility of risks and adverse events happening in the control groups is especially dire in our context, with challenges around accessibility to and cost of healthcare, as well as worrying health indices (for example, India has the highest number of neonatal deaths in the world, comprising 28% of the global burden) (4). Given the vulnerabilities existing in populations in the developing world, the utilisation of control groups in certain CRT designs has been questioned (5).

In conclusion, the paper read in conjunction with others in the series will provide a useful orientation to those interested in exploring this ethical grey zone in CRTs.

References

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