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The ethics of cluster-randomized trials requires further evaluation: a refinement of the Ottawa Statement

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Abstract

Objectives: The Ottawa Statement is the first guidance document for the ethical and scientific conduct of cluster-randomized trials (CRTs). However, not all recommendations are straightforward to implement. In this paper we will reflect in particular on the recommendation on identifying human research subjects and the issue to what extent the randomization process should be disclosed if there is a risk of contamination.

Study Design and Setting: The Ottawa Statement was thoroughly evaluated within a multidisciplinary research team, consisting amongst others of epidemiologists and ethicists.

Results: Patients in a CRT may also be considered as research subjects if they are indirectly affected by the studied interventions in a CRT. Second, health care workers are research subjects in CRTs but have a different moral status compared with ordinary research participants. This different status has implications for withdrawal and the choice of the primary objective. Third, modified informed consent for CRTs may be obtained when researchers can demonstrate that disclosure of the randomization process would affect the validity of a CRT.

Conclusion: Recommendations of the Ottawa Statement on identifying the research subject and providing informed consent can and should be refined.

Keywords: Cluster-randomized trials; Disclosure of randomization; Research participants; Informed consent; Research ethics; Modified informed consent

1. Introduction

Ethical guidelines on human subject's research have scarcely addressed the conduct of cluster-randomized trials (CRTs) [1,2]. Therefore, the recently published Ottawa Statement and its background articles on the ethical design and conduct of CRTs are of value to all who conduct, regulate, and review CRTs [3−8]. However, some recommendations are not straightforward to implement, such as who the intended recipient of the research intervention is and what should be disclosed in the informed consent process [9]. In this article, we comment on these issues and give suggestions for refining the Ottawa Statement.

2. Methods

The issues that we comment on in this article were identified by thorough reflection and discussion within our project team, which we established in 2012 to evaluate innovative trial designs for medical research. This project team consists of bioethicists, epidemiologists, health economists, and statisticians employed in the University Medical Center Utrecht. To better grasp the ethical issues in CRTs, we also jointly reflected on a recent CRT that one

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What is new?

Key findings

- The Ottawa Statement on cluster-randomized trials (CRTs) has provided unique guidance for the ethical conduct of CRTs but is not always straightforward to implement

What this adds to what was known?

- Patients should not only be regarded as research subjects when they are the direct target of an intervention, but also when they are indirectly affected.
- Health care workers (HCWs) have a different moral status than ordinary research participants which implies a higher threshold for withdrawal of HCWs and has implications for the choice of the primary objective of CRTs.
- Researchers may ask patients for modified informed consent in cases where researchers can demonstrate that disclosure of the randomization process would affect the validity of a CRT.

What is the implication and what should change now?

- Several recommendations of the Ottawa Statement on CRTs need to be refined.

of us has performed, the impact trial [10], to which we will return below. The identified issues were normatively evaluated by critical reflection within our group and by application of secondary literature. The issues we identified overlap with the themes that Ruth Macklin has recently identified as problematic: ''whether both health care workers (HCWs) and patients should be considered subjects in the trials, whether there is a need to obtain informed consent from both groups, and whether equipoise is still necessary'' [9]. We will elaborate on these issues by further ethical reflection. Apart from the recent review of Macklin, thus far, there have been no other reviews of the Ottawa Statement. The issues that we comment on are explained in detail below and are summarized in Box 1.

3. Identifying research participants

3.1. Indirectly affected patients are research participants

According to the Ottawa Group, not only patients but also HCWs can be research participants. Recommendation 3 states that ''a research participant can be identified as an individual whose interests may be affected as a result of study interventions or data collection procedures, that 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'' [3].

The Ottawa Group explains that if HCWs receive an educational or behavioral intervention to improve care for their patients, the patients of these HCWs are not research participants because HWCs in this situation are ''still expected to act in the best interests of [their] patients and in accordance with professional practice standards'' [3]. However, it is questionable whether this claim is correct. For example, consider the impact trial.

The impact trial was a single-center CRT in which the hypothesis was tested that implementation of a prediction model for postoperative nausea and vomiting (PONV) will lower the PONV incidence by stimulating anesthesiologists to administer a more risk-tailored prophylaxis to patients. The study was cluster-randomized on the physician-level to avoid contamination. All (79) anesthesiologists working in this center were randomized and either exposed to automated risk calculations for PONV or would give care as usual. Together these anesthesiologists treated 12,032 patients. The primary outcome was the effect of exposure to the patient-specific predicted risk of PONV. The secondary outcome was the change in physician behavior (administration of risk-dependent PONV prophylaxis) caused by exposure to predicted risks. Anesthesiologists of the intervention group were informed about the allocation status of other colleagues in their group to promote how to use the model and its predictions. They were instructed to avoid discussing PONV with the anesthesiologists randomized to the control group. At the start of the study, the control group was only informed about the goal of the study and their randomization status. None of the physicians gave informed consent. The ethics committee provided a waiver for individual informed consent of patients because the prediction rule provides physicians with evidence-based information. Informed consent for data collection was obtained [10].

If the principles of the Ottawa Statement are applied, patients are human research subjects in the impact trial because the fourth condition of recommendation 3 applies: patients' records are used to measure the effect of the prediction rule. The first condition of recommendation 3 will most likely not apply because patients are the indirect target of the prediction rule that anesthesiologists have been asked to apply. The second condition will probably also not apply because the patients will receive evidence-based care and are therefore not the direct target of an experimental manipulation. Finally, the third condition obviously does