

COMMENTARY

The ethics of cluster randomized trials: response to a proposal for revision of the Ottawa Statement

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Abstract

Background and Objectives: Cluster randomized trials are commonly used to evaluate public health, knowledge translation, and health service interventions. Cluster trials raise novel ethical issues, however, and the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials* (2012) provides researchers and research ethics committees with needed guidance. In this journal, van der Graaf et al. reflect on the *Ottawa Statement* and propose three revisions. In this paper, we respond to each of these proposed revisions.

Results: First, van der Graaf et al. argue that patients who are merely indirectly affected by study interventions ought nonetheless to be considered research participants. We disagree. So long as the practice change is evidence based and the physician continues to make individualized judgments regarding patient care, patient liberty and welfare interests are not substantially affected. Second, although they agree that health providers who are targeted are research participants, they argue that such providers ought to be treated differently and should not be allowed to withdraw from a study too easily. In our view, this position fails to weigh adequately the potential for coercion and harms faced by employees in research. Third, they argue that the potential for bias may require blinding participants to allocation and study interventions in the consent process of a cluster trial. We agree on this point and support this approach in a limited set of cases.

Conclusion: While we reject two of van der Graaf et al.'s proposed revisions, we agree that further guidance on informed consent and study bias is needed. © 2019 Elsevier Inc. All rights reserved.

Keywords: Cluster randomized trial; Research ethics; Informed consent; Research ethics committee; Guidelines

Cluster randomized trials (CRTs) are increasingly used in health research to evaluate public health, knowledge translation, and health service interventions. Because of features of their design, CRTs pose challenges to the interpretation of ethics guidelines and regulations. As a result, researchers and research ethics committees need clear guidance on the ethics of CRTs. In 2012, our research group published the first international ethical guidelines for CRTs, the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials* [1]. The *Ottawa Statement* has been widely cited

and has influenced policy in the United Kingdom, the United States of America, and internationally [2–4].

In the pages of the *Journal of Clinical Epidemiology*, van der Graaf et al. reflect on the *Ottawa Statement* and propose three revisions [5]. First, patients ought to be considered research participants when “they are indirectly affected as the result of an intervention targeted at a (health provider)” [5]. Second, health providers have a “different moral status than ordinary research participants, which implies a higher threshold for withdrawal” [5]. Third, aspects of the CRT, including randomization, should not be revealed in the consent process when “disclosure of the randomization process would affect the validity of [the] CRT” [5]. In this commentary, we respond to each of these proposals.

1. Patients as research participants

First and foremost, the task of the research ethics committee is to protect the liberty and welfare interests of research participants. To do that job, participants must be

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What is new?**Key findings**

- The *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials* provides researchers and research ethics committees with key guidance.
- van der Graaf et al. propose three revisions to the *Ottawa Statement*: (1) patients indirectly affected by interventions should be considered research participants; (2) health providers who are research participants should be treated differently than other participants; and (3) changes to informed consent may be needed to prevent serious study bias.
- We argue that the first two proposals should not be supported but agree that informed consent may be modified when the risk of performance bias and attrition is demonstrably high.

What this adds to what is known?

- Cluster trials are complex studies in which the identification of research participants may be particularly challenging.
- Expanding the definition of research participants to include patients merely indirectly affected by an evidence-based practice change is too broad and will greatly expand the pool of research participants without significantly improving protections for them.
- Researchers and research ethics boards commonly fail to correctly identify health providers as research participants.

What is the implication and what should change now?

- Researchers and research ethics committees should take steps to ensure that health providers are correctly identified as research participants.
- When feasible, cluster trial participants should be blinded to the arm to which they have been allocated to prevent selection bias.
- When the risks of bias due to knowledge of intervention is demonstrably high, researchers may apply to the research ethics committee for an alteration of consent to blind participants to the intervention.

interest are randomized to one of the trial arms, they are intervened on according to the study protocol, and relevant outcome data are collected from them. Accordingly, all enrolled patients are research participants.

CRTs are complex, multilevel studies in which the units of randomization, intervention, and outcome may differ within the same study. As different groups of people may be involved in a CRT in differing ways, the identification of research participants is complicated. The *Ottawa Statement* observes that “research participants are those most directly affected by the conduct of research” and defines the participant as “an individual whose interests may be affected as a result of study interventions or data collection procedures” [1]. This definition is operationalized by four criteria, any one of which is sufficient to confer the status of participant. Thus, 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 [1].

This definition of research participant has implications for knowledge translation CRTs. When a knowledge translation intervention seeks to increase health provider uptake of evidence-based best practice, the health providers are research participants. Surprisingly, perhaps, patients of the health providers are not participants unless they are otherwise intervened on, interacted with, or their identifiable health data are collected. When patients are merely indirectly impacted by the study intervention, their liberty and welfare interests are not substantially affected. Their physician continues to make individualized judgments regarding their care, and they remain free to discuss treatment options, request a different treatment, or reject all options.

Although van der Graaf et al. generally support the *Ottawa Statement*'s approach to the identification of research participants, they argue that patients who are only indirectly affected by interventions for which health providers are the intended recipients should nonetheless be considered participants. They appeal to the IMPACT trial, a single-center CRT in which anesthesiologists are randomized to receive (or not receive) an automated calculation for the risk of postoperative nausea and vomiting for each patient in their care (see [Text Box 1](#)) [6]. Applying the *Ottawa Statement*, they conclude that the anesthesiologists are research participants as they are “directly intervened on” by the study intervention, but patients are only research participants insofar as their data are collected; patients do not fulfill the first criterion because they are only “the indirect target of the prediction rule” [5].

clearly and accurately identified. In individually randomized controlled trials, the identification of participants is straightforward. Typically, patients with the condition of

Text Box 1 The IMPACT trial

Aim: The IMPACT trial seeks to evaluate implementation of a prediction model for postoperative nausea and vomiting [6]. The hypothesis is that use of the model will lower the incidence of nausea and vomiting in patients when anesthesiologists administer prophylaxis in a manner tailored to patient risk.

Background: Nausea and vomiting in patients after surgery is an important clinical issue. Current guidelines recommend that at-risk patients be given prophylaxis in the operating room by the anesthesiologist. A number of prediction models for nausea and vomiting exist, but their impact on patient outcomes has not been established. “[C]omparative randomized studies assessing the actual impact of risk-dependent prophylaxis on the incidence of postoperative nausea and vomiting are rare. Without such studies, one still cannot be confident that...prediction models will outperform clinical judgment and improve patient outcomes” [6].

Design: Parallel-arm cluster randomized trial. Permuted block randomization was used to stratify on anesthetic experience and subspecialty.

Study population: All anesthesiologists at a single center are randomized to receive either the study intervention or control condition. Each anesthesiologist’s patients constitute the clusters.

Study intervention: Postoperative nausea and vomiting prediction model: the prediction model was “originally developed in a population of a different university hospital...and had already been externally validated” [6]. The prediction model was “updated and optimized for implementation” at the study center [6]. Anesthesiologists in the intervention arm were provided with educational sessions throughout the trial but were free to prescribe antiemetics to patients as they saw fit. They were informed of the allocation status of their colleagues and encouraged to discuss the trial with others in the intervention arm, but not those enrolled in the control arm. They also received individualized feedback on the incidence of nausea and vomiting in their patients, the incidence for the hospital as a whole, and the amount of antiemetics prescribed.

Control condition: Usual care. Anesthesiologists in the control arm were only informed of the goals of the trial and their enrollment in the control arm.

Data collection: The main study outcomes are patient nausea and vomiting after surgery and antiemetics administered by anesthesiologists intraoperatively.

Ethics: The principal investigator informed the anesthesiologists of the arm to which they had been allocated, but their informed consent was not obtained. The research ethics committee granted a

waiver of consent for patients on the grounds that physicians were only provided “evidence-based information” [6].

Results: There were no differences in the incidence of postoperative nausea and vomiting between the two study arms. Anesthesiologists in the intervention arm administered more antiemetics and provided more risk-tailored care compared with those in the control group.

van der Graaf et al. believe this conclusion is problematic for three reasons. First, they argue that at the start of the study it is not known whether the intervention “is superior or inferior to the effects of the control” and, as a result, the care the patients “receive is under study” [5]. Second, “because this trial was undertaken to have an effect on patients, it seems morally problematic to only having this trial reviewed for using patients’ data” [5]. Third, “indirectly affected patients are not considered research participants, which implies that their informed consent may be too easily ignored, in particular where it could have been sought relatively easily” [5].

Unfortunately, the IMPACT trial does not illustrate well the concerns raised. First, we believe that correct application of the *Ottawa Statement* criteria would identify both patients and providers as research participants. The experimental intervention is not a knowledge translation intervention to promote the uptake of evidence-based practice. As stated in the trial publication, this was an implementation trial to test the effectiveness of the prediction rule when implemented in clinical practice. The study seeks to determine whether the intervention will “improve patient outcome by lowering the incidence of (postoperative nausea and vomiting), as a result of an increase in risk-tailored antiemetic treatment by physicians” [6]. Thus, the effectiveness of the rule is not yet established and, accordingly, it is experimental at the patient level (see Text Box 1).

Second, van der Graaf et al. seem to be suggesting that if patients are not the intended recipients of the intervention, it need not be reviewed. We disagree. According to the *Ottawa Statement*, a research ethics committee must review any CRT involving human participants (recommendation 2) [1]. There is no disagreement that the IMPACT trial involves two types of participants, the anesthesiologists and their patients (as their data are collected). Consequently, a research ethics committee must review the whole IMPACT trial.

Third, van der Graaf et al. worry that if patients indirectly affected by the study intervention are not considered research participants, their “informed consent may be too easily ignored” [5]. This strikes us as question begging. If patients are correctly classified as not the “intended recipient[s]” of the study intervention, then it is hard to see why their informed consent to the intervention is

required. (Their consent may nonetheless be required for data collection). For the reasons outlined previously, we believe that the patients in the IMPACT trial are research participants because they (along with the anesthesiologists) are the intended recipients of the study intervention and their private health data are collected. Thus, according to the *Ottawa Statement*, their informed consent is required unless a research ethics committee grants a waiver of consent (recommendation 4) [1].

2. Health providers as research participants

In CRTs evaluating knowledge translation or health service interventions, health providers are commonly the intended recipients of study interventions. Accordingly, health providers are frequently research participants in CRTs. This means they are entitled to the protections offered by research guidelines, research ethics committee review, and informed consent. Unfortunately, in our experience, researchers and research ethics committees commonly fail to identify health providers as research participants. Thus, the *Ottawa Statement* says that when they are participants, health providers are “entitled to ethical protections,” including their informed consent unless conditions for a waiver of consent obtain (recommendation 7) [1].

Indeed, the IMPACT trial seems to illustrate the phenomenon of neglecting to see health providers as participants. In no case was the informed consent of health providers obtained. Despite the fact that the study intervention included educational sessions for health providers, the automated prediction model and audit and feedback of provider practice, ethics review seems to have focused only on a waiver of informed consent for patients. According to the trial publication:

As the decision support tool...only provided evidence-based information to physicians, the institutional ethical review board waived the need for individual informed consent and approved the study protocol [6].

To grant a waiver of consent, the research ethics committee must ensure that requiring informed consent would render the study infeasible and that participation poses only minimal risk. Although one could argue that a waiver is appropriate for 12,032 patients in the IMPACT trial, it is difficult to see how it is appropriate for the health providers. Indeed, the principal investigator, who informed all anesthesiologists of their enrollment in the study, could have obtained their informed consent to participation at that time.

van der Graaf et al. argue that health providers in CRTs are “not morally equivalent to ordinary research (participants)” and they have a “different moral status” [5]. Although CRTs may have a broad impact on patients, the impact on health providers is restricted to their “professional

behavior” [5]. So long as health providers remain free to make “professional judgments on the best interests of the patient,” their autonomy is not infringed. Indeed, health providers have an obligation to promote patient health and, as a result, they “should not be allowed to withdraw easily when approached to participate in trials that aim to improve the health and well-being of patients” [5]. However, van der Graaf et al. point out that this does not mean that health providers should be “forced to participate...[T]heir informed consent...should be obtained where feasible” [5].

The concept of moral status identifies those to whom we owe regard in moral decision making. If a being has moral status, then we must consider its interests when we make decisions that may affect it. The regard we owe research participants does not merely flow from research guidelines or regulations. All people possess a right to be free of medical or scientific experimentation without informed consent [7]. This applies no less to health providers than patient in CRTs; their moral status is, we believe, the same. van der Graaf et al. further suggest that health providers acting in their professional role are impacted less by participation in a CRT. In other words, such participation is less consequential, so long as it is in line with the health providers’ duties as employees. But, this ignores the harms that may accrue to employees in research, including the revelation of substandard performance or reputational harms. Furthermore, their view fails to acknowledge that the voluntariness of consent from employees may be undermined in a hierarchical organization. Indeed, employees are increasingly recognized as vulnerable research participants requiring additional protection, not less protection [8].

We do not agree that standards for informed consent for health providers in CRTs should differ from those for other research participants. Although health providers do have an obligation to improve the health and well being of their patients, this does not, in our view, imply an obligation to participate in research. If it were known upfront that the study intervention is effective, the CRT would violate equipoise and be unethical. Even if one accepts that health providers have a *prima facie* obligation to participate in research (and we do not), this is a reason for them to say “yes” when approached for consent; but it does not relieve researchers of their obligation to seek health providers’ informed consent. Finally, the suggestion that informed consent should be obtained but that one “should not be allowed to withdraw easily” undermines health provider autonomy.

3. In the informed consent process, what should be disclosed to participants?

The ethical principle of respect for persons grounds the requirement to seek the informed consent of research participants. The *Ottawa Statement* makes clear that the informed consent of participants in CRTs must be obtained, unless conditions for a waiver of consent obtain (recommendations 4 and 7) [1]. Participants must be informed of

“the purpose of the study, study interventions and data collection procedures, the potential benefits and risks of study participation, and alternatives to participation” [1]. Thus, generally “informed consent refers to randomization, study interventions, and data collection procedures” [1]. As explained previously, CRTs may involve different groups of people in differing ways. Thus, in a single CRT, one group (e.g., health providers) may be the intended recipients of the study interventions, whereas data collection procedures target another group (e.g., patients). In these cases, “different participants may need to provide consent to different elements” [1].

If seeking informed consent to study interventions or data collection procedures is not feasible, researchers should ask the research ethics committee to grant a waiver or alteration of consent (recommendation 6) [1]. The researcher must demonstrate that (1) obtaining informed consent is infeasible and (2) study participation poses only minimal risk. Feasibility may depend on “cluster size, proximity of cluster members (and thus ease of contact), complexity of the consent process, research infrastructure (such as the number of local health workers available to approach cluster members), and research funding” [1]. A commonly expressed concern is that information provided in the consent process will lead to contamination. In such cases, the *Ottawa Statement* recommends “an alteration of the consent process (such as blinding participants to their allocation status)” [1]. It goes on to caution that “different consent procedures in the intervention and control arms of the trial may lead to bias” [1]. Different consent procedures may lead to differential recruitment across trial arms with, for instance, healthier participants self-selecting for the intervention arm [9].

van der Graaf et al. believe that “further clarification of what should be disclosed” in the informed consent process in CRTs is required and we agree [5]. When the intervention is delivered at the cluster level, it may be impossible for cluster members to avoid the study intervention. Provided that the intervention poses only minimal risk, the *Ottawa Statement* supports the use of a waiver of consent. CRTs with individual level interventions pose a more difficult challenge. van der Graaf et al. point out—correctly—that “if people in the control arm learn about the intervention administered in the experimental arm, they may change their behavior thereby compromising the validity of research outcomes” [5]. They propose the use of “modified informed consent,” in which “randomization should not be disclosed” [5]. Thus, information about the study and control interventions is withheld. They believe that modified consent will better protect CRTs from contamination and set out several criteria for its use. We agree with van der Graaf et al. that this approach is justified in some cases. In the following, we describe two approaches to informed consent that are responsive to concerns about bias when patients must be recruited after cluster randomization.

In the first approach, cluster members, when approached for study enrollment, can provide their informed consent to study participation unaware of the arm to which their cluster has been allocated. Preferably, those recruiting and approaching cluster members for consent are blinded to the allocation status of the cluster. Indeed, the informed consent would closely resemble that for an individually randomized controlled trial, meaning that participants are fully informed about the study and control interventions but their allocation status is concealed. This approach to informed consent effectively eliminates the risk of recruitment bias. Although allocation status is concealed in the consent process, it does not require that the CRT proceeds in a blinded fashion. Insofar as cluster members can determine over time the arm to which they have been allocated, contamination remains possible, but selection bias may be avoided in an intention to treat analysis.

We believe that concealing allocation during the recruitment and informed consent process can help preserve trial validity while protecting participant autonomy in most cases. It does not protect against all forms of bias, however. Once trial participants learn of their allocation (e.g., when the intervention is delivered), their behavior may change (performance bias) or they may withdraw from the trial (attrition). Thus, knowledge of being in a trial and which intervention they have received can lead to bias because of deviations from the intended intervention. These concerns cannot be dealt with in a simple analysis.

When there are substantial concerns of bias due to lack of blinding, researchers should apply to the research ethics committee for an alteration of consent. They must demonstrate that (1) obtaining informed consent with all of the required elements (i.e., obtaining informed consent while fully revealing the study hypotheses and intervention and control conditions) is incompatible with the scientific ends of the study (i.e., infeasible) and (2) study participation poses only minimal risk.

In this second approach to informed consent, participants will ideally be recruited by individuals blinded to their allocation, and given similar information about the trial at the time of recruitment and at the time of intervention delivery. This means the exact nature of the study hypotheses is not revealed and participants will not know whether they received the study intervention or control. This is, we believe, van der Graaf’s “modified informed consent” proposal. We agree with van der Graaf et al. that participants must be told they are participating in a trial and that information is being withheld from the consent process to protect the scientific validity of the study [5]. To prevent unblinding, the control arm may require some minimum level of intervention to avoid problems such as resentment and study withdrawal. After the study is completed and the results analyzed, participants should be informed of the details of the trial, the intervention to which they were allocated, and the results of the study [5]. We believe this second approach to informed consent will be useful in a

minority of cases in which risks of performance bias and attrition are demonstrably high.

4. Conclusion

van der Graaf et al. propose three revisions to the *Ottawa Statement*. In our response, we discuss the merits of each proposal. We believe dialog about the *Ottawa Statement* has identified important issues. First, determining when health providers and patients participating in knowledge translation and health service CRTs ought to be considered research participants can be complex. Further guidance on this question would assist researchers and research ethics committees. Second, researchers and research ethics committees commonly fail to correctly identify health providers as research participants in CRTs. Awareness of this must be raised through education and outreach. When they are research participants, health providers have a right to the protections afforded by research ethics committee review and informed consent. Third, and finally, the seriousness of different sources of bias associated with informed consent procedures requires attention from researchers, research ethics committees, and ethicists. We outline two approaches to informed consent in CRTs: one involving blinded recruitment of participants, which we believe is consistent with standard informed consent and another (in line with van der Graaf's proposal) involving blinded recruitment and intervention in cases where risks of bias due to knowledge of the intervention are demonstrably high, requiring research ethics committee approval for an alteration of consent.

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