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Gaps in the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*: a citation analysis reveals a need for updated ethics guidelines

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Abstract

Background Although commonly used to evaluate health interventions, cluster randomized trials raise difficult ethical issues. Recognizing this, the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*, published in 2012, provides 15 recommendations to address ethical issues across seven domains. But due to several developments in the design and implementation of cluster randomized trials, there are new issues requiring guidance. To inform the forthcoming update of the *Ottawa Statement*, we aimed to identify any gaps in the *Ottawa Statement* discussed within the literature.

Methods We searched Google Scholar, Scopus, and Web of Science using the 'cited by' function on 11 November 2022. We included all types of publications, including articles, book chapters, commentaries, editorials, ethics guidelines, theses and trial-related publications (i.e., primary reports, protocols, and secondary analyses), that cited and engaged with the *Ottawa Statement*, the *Ottawa Statement* précis, or one or more of its four background papers. Data were extracted by four reviewers working in rotating pairs. Reviewers captured relevant text verbatim and recorded whether it reflected a gap relating to one or more of the *Ottawa Statement* domains. Using a thematic analysis approach, semantic coding was used to summarize the content of the data into distinct gaps within the *Ottawa Statement* domains, which was subsequently expanded in an inductive manner through discussion.

Results The qualitative analysis of the text from 53 articles resulted in the identification of 24 distinct gaps in the *Ottawa Statement*: 4 gaps about justifying the cluster randomized design; 2 gaps about research ethics committee review; 3 gaps about identifying research participants; 4 gaps about obtaining informed consent; 3 gaps

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about gatekeepers; 6 gaps about assessing benefits and harms; 1 gap about protecting vulnerable participants; and 1 gap about equity-related issues in cluster randomized trials.

Conclusion Identifying 24 gaps reveals a need to update the *Ottawa Statement*. Alongside additional gaps identified in ongoing empirical work and through engagement with our patient and public partners, the gaps identified through this citation analysis should be considered in the forthcoming *Ottawa Statement* update.

Keywords Research ethics, Ethics guidelines, Citation analysis, Research ethics committee review, Informed consent, Benefit-harm assessment, Vulnerability

Background

When designing a randomized trial, choosing the appropriate unit of randomization is critical. Researchers may choose to randomize participants individually to intervention or control conditions, or to randomize intact groups called clusters—e.g., communities, hospitals, schools. Choosing a cluster randomized trial (CRT) is often essential for evaluating health policy, health systems, and public health interventions [1]. However, CRTs raise difficult ethical issues [2]. For instance, since the units of randomization, intervention, and outcome measurement may differ within a single CRT, the identification of research participants is complicated [3]. Further, clusters are commonly randomized before participants can be identified and recruited. In such cases, it is unclear who should provide consent [4], and post-randomization recruitment increases risks of bias that can undermine the scientific validity of results [5]. And when the intervention is delivered to clusters as opposed to cluster members, it may be difficult for cluster members to avoid being exposed to the intervention, undermining people's ability to refuse study participation.

As most research ethics guidelines were written with individually randomized trials in mind, their application to CRTs is not straightforward. This was the impetus for the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*, the first internationally recognized ethics guidance document specific to CRTs [6]. Published in 2012, the *Ottawa Statement* offers 15 recommendations across seven ethical domains (see Table 1): justifying the cluster randomized design; research ethics committee review; identifying research participants; obtaining informed consent; gatekeepers (i.e., people who are positioned to protect the interests of clusters and cluster members, such as medical directors, school principals, or village leaders); assessing benefits and harms; and protecting vulnerable participants.

Since its publication, there have been developments in CRTs and their use which have created gaps in ethics guidance. For instance, trialists increasingly use the stepped-wedge design, in which all clusters begin in the control condition and crossover to the intervention condition at randomly assigned timepoints, to evaluate the

implementation of health service or policy interventions [7]. However, it is debated whether it is ethically permissible to conduct a stepped-wedge CRT when evidence has accumulated concerning an intervention's efficacy [8–10]. Trialists are also designing CRTs with a waiver of consent to increase the pragmatism of their trials [11], but whether waivers are appropriate in CRTs to achieve the ends of pragmatism is contested. Moreover, the authors of the *Ottawa Statement* recognize the need for further engagement with community partners, especially in low-resource settings, to identify issues requiring guidance.

To address these and other gaps in ethics guidance, it is time to update the *Ottawa Statement*. As a first step in the process to update the *Ottawa Statement* [12], this review of the literature aims to identify and analyze articles that cite the *Ottawa Statement* [6], the *Ottawa Statement* précis (i.e., brief summary report) [13], or one or more of the *Ottawa Statement's* four background papers [3, 4, 14, 15]. The objective of this citation analysis is to summarize gaps in the *Ottawa Statement* discussed within the literature that should be addressed in the forthcoming update.

Methods

Search strategy

Google Scholar, Scopus, and Web of Science databases were searched using the 'cited by' function on 11 November 2022.

Inclusion and exclusion criteria

Given our interest in identifying any gaps in the *Ottawa Statement*, we considered all types of publications that cited and engaged with either the *Ottawa Statement*, its précis, or one or more of its four background papers. This included articles, book chapters, commentaries, editorials, ethics guidelines, theses, and trial-related publications (i.e., primary reports, protocols, secondary analyses). Abstracts, conference presentations, and articles published in a language other than English were excluded. Publications were also excluded if they merely cited (i.e., did not engage with) the *Ottawa*

Table 1 The *Ottawa Statement* recommendations; table reproduced from original source [6].

Ethical Domain	#	Recommendation
Justifying the cluster randomized design	1	Researchers should provide a clear rationale for the use of the cluster randomized design and adopt statistical methods appropriate for this design.
Research ethics committee review	2	Researchers must submit a CRT involving human research participants for approval by a research ethics committee before commencing.
Identifying research participants	3	Researchers should clearly identify the research participants in CRTs. 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. Unless one or more of these criteria is met, an individual is not a research participant.
Obtaining informed consent	4	Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a research ethics committee under specific circumstances.
	5	When participants' informed consent is required, but recruitment of participants is not possible before randomization of clusters, researchers must seek participants' consent for trial enrollment as soon as possible after cluster randomization—that is, as soon as the potential participant has been identified, but before the participant has undergone any study interventions or data collection procedures.
	6	A research ethics committee may approve a waiver or alteration of consent requirements when (1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.
	7	Researchers must obtain informed consent from professionals or other service providers who are research participants unless conditions for a waiver or alteration of consent are met.
Gatekeepers	8	Gatekeepers should not provide proxy consent on behalf of individuals in their cluster.
	9	When a CRT may substantially affect cluster or organizational interests, and a gatekeeper possesses the legitimate authority to make decisions on the cluster or organization's behalf, the researcher should obtain the gatekeeper's permission to enroll the cluster or organization in the trial. Such permission does not replace the need for the informed consent of research participants.
	10	When CRT interventions may substantially affect cluster interests, researchers should seek to protect cluster interests through cluster consultation to inform study design, conduct, and reporting. Where relevant, gatekeepers can often facilitate such a consultation.
Assessing benefits and harms	11	The researcher must ensure that the study intervention is adequately justified. The benefits and harms of the study intervention must be consistent with competent practice in the field of study relevant to the CRT.
	12	Researchers must adequately justify the choice of the control condition. When the control arm has usual practice or no treatment, individuals in the control arm must not be deprived of effective care or programs to which they would have access, were there no trial.
	13	Researchers must ensure that data collection procedures are adequately justified. The risks of data collection procedures must (1) be minimized consistent with sound design and (2) stand in reasonable relation to the knowledge to be gained.
Protecting vulnerable participants	14	Clusters may contain vulnerable participants. In these circumstances, researchers and research ethics committees must consider whether participants additional protections are needed.
	15	When individual informed consent is required and there are individuals who may be less able to choose participation freely because of their position in a cluster or organizational hierarchy, research ethics committees should pay special attention to recruitment, privacy, and consent procedures for those participants.

Statement, its précis, or a background paper (e.g., systematic reviews citing the *Ottawa Statement* to explain their rationale or methods, qualitative studies citing the *Ottawa Statement* to inform interview guides or surveys, and methods-focused opinion pieces citing the *Ottawa Statement*). Engagement was defined as either providing an argument that criticizes or supports at least one *Ottawa Statement* recommendation

or providing a reason to believe the *Ottawa Statement* lacks guidance.

Article selection

Since title and abstract screening is not possible in a citation analysis, all identified records were uploaded to Covidence software [16]. An initial, high-level full text screening was completed by two reviewers (JFS, SGN) to confirm eligibility (i.e., exclude abstracts, conference

presentations, and non-English articles). Four reviewers (JFS, KC, MT and SGN) reviewed all articles in two rotating pairs of reviewers per article to exclude records that merely cited the *Ottawa Statement*, its précis, or a background paper. Discrepancies were resolved through discussion. Two reviewers with expertise in ethical analysis and philosophical argumentation (CW, NBM) then conducted in-depth full-text screening of the potentially eligible articles to ensure all articles both cited and engaged with the *Ottawa Statement*, its précis, or a background paper, resolving discrepancies during regular consensus meetings.

Data extraction

A data extraction form was developed by four reviewers (CEG, CW, JdT, NBM), and was piloted and refined using three randomly selected eligible records. The final extraction form was uploaded into AirTable software [17]. The same four reviewers, working in rotating pairs, proceeded to extract data from all articles classified as engaging with the *Ottawa Statement*. For each article, the reviewers extracted the publication year, journal, country of first author, and whether any author of the publication was also an author of the *Ottawa Statement*, its précis, or one of its background papers. The reviewers then captured the text citing the *Ottawa Statement* verbatim and recorded whether this text or any of the accompanying discussion within the full publication reflected a gap relating to an *Ottawa Statement* recommendation, or not. The text was further categorized according to the relevant *Ottawa Statement* domain to which the discussion pertained; discussion of an issue outside the scope of an *Ottawa Statement* domain was classified as ‘other.’ Each article could discuss more than one domain. Discrepancies were resolved by all four reviewers in bi-weekly meetings.

Data analysis

Qualitative analysis proceeded iteratively throughout data extraction. Using a thematic analysis approach [18], semantic coding by four reviewers (CEG, CW, JdT, NBM) was used to summarize the content of the data into distinct gaps within the *Ottawa Statement* domains, which was subsequently expanded in an inductive manner through discussion. Identified gaps were presented to members of the research team involved in the *Ottawa Statement* update for feedback. Based on the discussion, a writing team (CEG, CW, JdT, MT, NBM) further refined and categorized the identified gaps. Following the completion of data extraction and qualitative analysis, one reviewer (CEG) analyzed the categorical variables using a descriptive analysis.

Patient and public involvement

Five patient and public partners are members of the international team tasked with updating the *Ottawa Statement*. One (MS) was involved in the reporting and dissemination of this study.

Results

Our search strategy identified 1,326 records. After duplicates were removed, 383 records underwent the initial high-level full text screening to confirm eligibility. Among these, 288 merely cited the *Ottawa Statement*, its précis, or a background paper, 15 additional duplicates were removed, 4 were non-English records, and 3 did not cite a relevant paper. After the in-depth full-text screening of the remaining 73 articles, 53 were classified as engaging with the *Ottawa Statement* and were retained for data extraction. See Fig. 1 for our flow diagram and Appendix A for a list of included publications.

Article characteristics

Table 2 presents the characteristics of the 53 articles. The first author of the articles were mostly from the United States (21, 40%), Canada (13, 25%), or the United Kingdom (8, 15%). Twenty-one (40%) articles had a co-author who is also an author of the *Ottawa Statement*, its précis, or one of its background papers. The following *Ottawa Statement* domains were discussed in the 53 articles: obtaining informed consent (37, 70%); identifying research participants (22, 42%); justifying the cluster randomized design (20, 38%); assessing benefits and harms (21, 40%); gatekeepers (14, 26%); research ethics committee review (13, 25%); and protecting vulnerable participants (7, 13%). Ten (19%) articles discussed issues that did not fall within an existing *Ottawa Statement* domain.

Gaps in the *Ottawa Statement*

Through a qualitative analysis of the 53 articles, 24 unique gaps were identified that cut across the seven *Ottawa Statement* domains or an “other” domain. In what follows, we proceed through each of these domains and report the particulars of the gaps using select quotations to reflect the range of views in the literature. Table 3 presents a summary of the identified gaps.

Justifying the cluster randomized design

Among the 20 articles that discussed the *Ottawa Statement*'s recommendations regarding justifying the cluster randomized design, 4 gaps were identified.

When is the choice to use a CRT design appropriately justified? There is broad agreement in the literature with the first recommendation of the *Ottawa Statement*, namely, that the choice to use a CRT design over

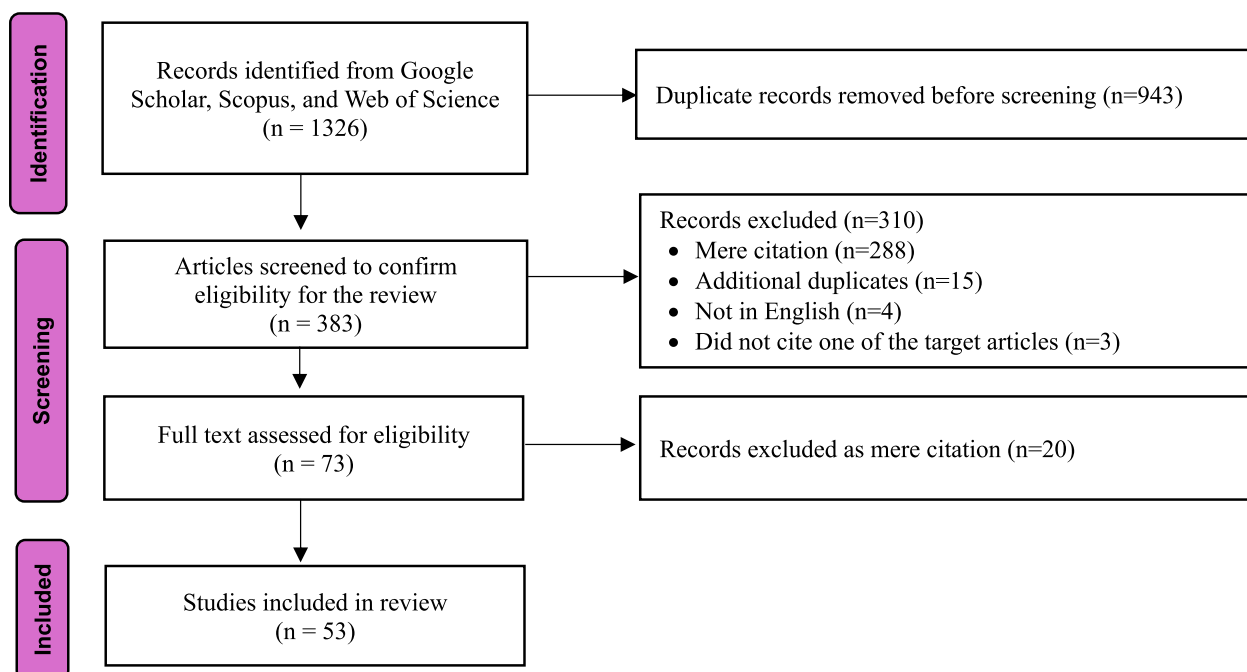


Fig. 1 Flow diagram

an individually randomized design should be justified. For instance, Choko and colleagues state, “As cluster randomized designs are statistically inefficient and prone to bias, their use requires justification” such as “administrative and logistical reasons, and concerns over contamination.” [19]. CRTs are statistically inefficient compared to individually randomized trials with the same number of participants since outcomes among cluster members are usually positively correlated. CRTs are also more prone to bias when participants are identified or recruited after clusters have been randomized. Wagman and colleagues also suggest that CRTs “are ideal when the intervention will be applied to entire communities...[and] when contamination between individuals in the same community is likely if they are randomized to different treatment arms.” [20].

Goldstein and colleagues agree that, as per the *Ottawa Statement*, “reasons for using cluster, rather than individual, randomization might include minimizing contamination, facilitating intervention implementation, enhancing adherence, administrative convenience, and reducing research costs.” [21]. They note, however, that reasons for using a CRT design track the level of intervention. Cluster-level interventions are delivered to clusters as a whole (e.g., mass media campaign) and cannot be evaluated using an individually randomized design. Individual-level interventions are delivered directly to cluster members (e.g., vaccines) and can be evaluated

using either an individually or cluster randomized design. When an intervention can be evaluated with either design, researchers should provide compelling practical or scientific reasons when cluster randomization is chosen given the statistical inefficiency and increased risks of bias in CRT designs compared to individually randomized designs. But “when administrative or logistical considerations, rather than scientific considerations, for adopting cluster randomization are invoked... evaluating their legitimacy may be difficult.” [21]. The *Ottawa Statement* could clarify when the use of CRT designs over individually randomized designs is appropriately justified.

Is pragmatism a reason to adopt a CRT design? Relatedly, some authors posit that a reason to adopt a CRT design is to increase pragmatism or enhance the external validity of a trial. For example, Rogers and colleagues state,

“Cluster randomised trials... are more economical to implement and can be scaled up readily across health services, allowing more efficient and equitable use of finite research resources. A major advantage of cluster randomised trials over individually randomised trials is that the former improve generalisability, as randomisation can include all individuals who would be eligible for an intervention and not just those who choose to participate.” [22].

Table 2 Characteristics of $N = 53$ articles included in our review

Characteristics	Frequency (%) $N = 53$
Publication year	
2012–2014	8 (15.1)
2015–2018	17 (32.1)
2019–2022	28 (52.8)
Median (Q1–Q3)	2019 (2015–2020)
Journal	
<i>Journal of Medical Ethics</i>	9 (16.9)
<i>Clinical Trials</i>	5 (9.4)
<i>Trials</i>	4 (7.5)
<i>American Journal of Bioethics</i>	3 (5.7)
<i>Journal of Clinical Epidemiology</i>	3 (5.7)
<i>Bioethics</i>	2 (3.8)
<i>Canadian Journal of Anesthesia</i>	2 (3.8)
<i>Hastings Center Report</i>	2 (3.8)
<i>Public Health Ethics</i>	2 (3.8)
Non-journal publication (e.g., book, policy document, thesis)	3 (5.7)
Other ^a	18 (33.9)
Country of first author	
United States	21 (39.6)
Canada	13 (24.5)
United Kingdom	8 (15.1)
Netherlands	3 (5.7)
Australia/New Zealand	2 (3.8)
India	2 (3.8)
Malawi	2 (3.8)
Switzerland	2 (3.8)
Was an author of the <i>Ottawa Statement</i> one of the co-authors?	
Yes	21 (39.6)
No	32 (60.4)
Engagement with the <i>Ottawa Statement</i> domains^b	
Domain 1: Justifying the cluster randomized design	20 (37.7)
Domain 2: Research ethics committee review	13 (24.5)
Domain 3: Identifying research participants	21 (39.6)
Domain 4: Obtaining informed consent	37 (69.8)
Domain 5: Gatekeepers	14 (26.4)
Domain 6: Assessing benefits and harms	20 (37.7)
Domain 7: Protecting vulnerable participants	7 (13.2)
Other	10 (18.9)

^a Other journals include the following: *American Journal of Kidney Diseases*; *Anesthesiology*; *BMC Medical Ethics*; *British Medical Journal*; *BMJ Global Health*; *British Educational Research Journal*; *Clinical Infectious Diseases*; *Contemporary Clinical Trials*; *Developing World Bioethics*; *Ethics & Human Research*; *Implementation Science*; *Journal of the American Medical Association*; *Journal of Law, Medicine & Ethics*; *Malta Medical Journal*; *Pediatric Drugs*; *Psychological Violence*; *Seminars in Neurology*; *Vaccine*

^b Multiple selection possible; frequencies do not add to 100%

Goldstein and colleagues point out that such claims “confuse the choice between individual and cluster randomization with the choice between an explanatory and a pragmatic trial design” and “while CRTs can be designed to address questions of both efficacy and effectiveness, they often include only a small number of clusters that

can severely limit their external validity, increase the risk of type I error, and lead to various forms of bias.” [23]. The *Ottawa Statement* could clarify the relationship between pragmatic trials and CRTs, and whether promoting pragmatism is a compelling reason to adopt a CRT design.

Table 3 Summary of identified gaps in the *Ottawa Statement*

Ethical Domain	Identified gaps	Considerations for the <i>Ottawa Statement</i> update
Justifying the cluster randomized design	<ol style="list-style-type: none"> 1. When is the choice to use a CRT design appropriately justified? 2. Is pragmatism a reason to adopt a CRT design? 3. Should an individual-level intervention adopted as a local policy be conceptualized as a cluster-level intervention? 4. What justifies using a stepped-wedge design? 	<ul style="list-style-type: none"> • Clarify when using CRT designs over individually randomized designs is appropriately justified • Clarify the relationship between pragmatic trials and CRTs, and whether the goal of promoting pragmatism is an adequate reason to adopt a cluster randomized design • Clarify the difference between cluster-level and individual-level interventions, and whether individual-level interventions adopted as a local policy constitute a cluster-level intervention • Provide guidance for when using a stepped-wedge design over a parallel-arm design is justified, and whether there may be ethical reasons to choosing the former
Research ethics committee review	<ol style="list-style-type: none"> 5. Is research ethics committee review required for CRTs evaluating government health programs? 6. When is research ethics committee review required in host and sponsor countries? 	<ul style="list-style-type: none"> • Clarify the scope of research ethics committee review required for CRTs that evaluate government health programs or policies • Provide guidance on when both host and sponsor country review in multinational CRTs is required
Identifying research participants	<ol style="list-style-type: none"> 7. When should professionals be considered research participants in a CRT? 8. Should professionals be offered less stringent protections when they are research participants in a CRT? 9. Who are 'research bystanders' in a CRT? 	<ul style="list-style-type: none"> • Clarify the conditions under which professionals meet the definition of research participants • Clarify the level of protection to which professionals are entitled when they are research participants in CRTs • Define 'research bystanders' and outline what protections they are owed in CRTs
Obtaining informed consent	<ol style="list-style-type: none"> 10. When should a CRT be considered minimal risk and infeasible to conduct with informed consent? 11. When is using an opt-out strategy for recruitment appropriate in CRTs? 12. What alternative consent approaches should be considered in CRTs? 13. When is assent required in a CRT? 	<ul style="list-style-type: none"> • Provide details on when the criteria justifying alterations or waivers of consent requirements are met in CRTs • Provide guidance on when opt-out approaches to consent are justified in CRTs • Clarify the types of alternative consent approaches currently used in CRTs that may be appropriate • Provide guidance on when assent is required in CRTs involving children
Gatekeepers	<ol style="list-style-type: none"> 14. When can gatekeepers withhold permission for cluster enrolment? 15. Should language around consultation be updated? 16. When should gatekeepers be engaged? 	<ul style="list-style-type: none"> • Clarify the circumstances under which gatekeepers may justifiably withhold permission for the enrolment of their clusters into a CRT • Update language around consultation in CRTs to community engagement • Provide details on which gatekeepers should be engaged and when during the different phases of a CRT
Assessing benefits and harms	<ol style="list-style-type: none"> 17. How does equipoise apply to CRTs of health policy interventions? 18. How does equipoise apply to implementation research? 19. What level of care should be afforded to participants in the control arm of CRTs? 20. When is posttrial access to study interventions required in CRTs? 21. When should CRTs have a Data and Safety Monitoring Board? 22. When are interim analyses, stopping rules, and de-implementation strategies required? 	<ul style="list-style-type: none"> • Clarify how to apply the concept of equipoise to CRTs involving health policy interventions • Clarify how to apply the concept of equipoise to CRTs that are implementation research • Clarify the level of care that should be afforded to participants in the control arm of CRTs • Provide guidance on the ethical imperative to provide posttrial access to study interventions in CRTs • Provide guidance on when a Data and Safety Monitoring Board would be beneficial in CRTs and what should be under their purview • Include discussion of ethical considerations around interim analyses, stopping rules, and the de-implementation of interventions rolled out in stepped-wedge CRTs

Table 3 (continued)

Ethical Domain	Identified gaps	Considerations for the Ottawa Statement update
Protecting vulnerable participants	23. How should vulnerability be defined?	<ul style="list-style-type: none"> • Update the definition of vulnerable research participants and explain the individual and contextual features that may confer vulnerability status
Other	24. How should issues related to equity, diversity, and inclusion be addressed in CRTs?	<ul style="list-style-type: none"> • Provide guidance on equity-related issues in CRTs, particularly those conducted in low-resource settings

Should an individual-level intervention adopted as a local policy across clusters be conceptualized as a cluster-level intervention? As explained above, the justification for choosing a CRT design to evaluate a cluster-level intervention is simple: cluster-level interventions cannot be evaluated with an individually randomized design because the intervention is not delivered to cluster members. But in some CRTs, individual-level interventions are adopted as a local policy across clusters that applies to all cluster members (e.g., restricted versus liberal use of benzodiazepines for all patients undergoing cardiac surgery) [24]. While individual-level interventions (e.g., drugs) are delivered directly to cluster members in these trials, researchers argue that “patients cannot choose to avoid [the policy intervention] because the intervention is applied at the level of the healthcare environment and not that of the patient.” [24]. But Goldstein and colleagues question whether adopting an intervention as a local policy should be conceptualized as a cluster-level or individual-level intervention since improper conceptualization obscures the ethical analysis; for instance, “a waiver of consent may apply to cluster-level interventions, provided they pose only minimal risk to participants. Generally, however, in the case of individual-level interventions, informed consent is required.” [23]. The *Ottawa Statement* could clarify the difference between cluster-level and individual-level interventions, and whether individual-level interventions adopted as a local policy constitute a cluster-level intervention.

What justifies using a stepped-wedge design? While there are various methodological reasons for using a stepped-wedge CRT design [25], this design is susceptible to increased risks of bias compared to the standard parallel-arm CRT design. The *Ottawa Statement* does not provide guidance on what justifies using a stepped-wedge design over a more robust parallel-arm design. Moreover, it is contested whether ethical reasons justify using the stepped-wedge design. For example, Gopichandran and colleagues state,

“[Cluster randomized trials] are often used in health systems research, but when a public health intervention is known to be effective, withholding the intervention from those randomized to the control arm is ethically problematic. As a compromise, a stepped-wedge approach is sometimes justified to address this dilemma.” [8].

Federico and colleagues express a more cautious view about the justification for the stepped-wedge design. They claim that “ethical concerns about randomly assigning patients to control arms, thus denying them the foreseen benefits of an intervention, are often cited as one of

the primary motivations for choosing [a stepped-wedge] design, but such concerns should not alone be used to justify this study design.” [9].

However, Binik asserts that “while the stepped wedge design is ethically permissible, and may be supported by socio-political or logistical reasons, it offers no ethical advantage over parallel cluster trials or individually randomized controlled trials.” [10] In her view, if the evidence suggests the intervention under investigation is likely to do more good than harm, then withholding or delaying its delivery for research purposes would be unethical. The *Ottawa Statement* could provide guidance for when using a stepped-wedge design over a parallel-arm design is justified, and whether there may be ethical reasons to choosing the former.

Research ethics committee review

Among the 13 articles that discussed the *Ottawa Statement’s* recommendations regarding research ethics committee review, 2 gaps were identified.

Is research ethics committee review required for CRTs evaluating government health programs? The *Ottawa Statement* holds the presumption that researchers must submit a CRT involving human research participants for research ethics committee approval before commencing [6]. But this recommendation is disputed. For example, Watson and colleagues argue that research ethics committee review is too burdensome and unnecessary for CRTs evaluating government programs as it may “obstruct, interfere with or prevent important research and learning without providing any further protections to research participants.” [26]. They argue that government program implementation “would occur whether or not there were any concurrent, coincident, or otherwise related research activities,” and contend that a research ethics committee’s “oversight should be limited to where the [researcher] has responsibility,” [27] such as obtaining research ethics committee approval “for all the things they do in their role as researcher [including] data collection [and] analysis.” [26].

Weijer and Taljaard respond that the scope of research ethics review is not defined by researcher responsibility or control; it “is defined by the protection of research participants.” [28]. They contend that “the government does not implement a program as usual. Rather, researchers collaborate with the government to randomise provinces, communities, neighbourhoods or hospitals to intervention or control conditions in order to rigorously evaluate the program.” [28]. Since the choice of a CRT design clearly impacts the interests of research participants, Weijer and Taljaard conclude that research ethics

committee review of both randomization and the relevant government program will almost always be necessary. The *Ottawa Statement* could clarify the scope of research ethics committee review that is required for CRTs evaluating government health programs or policies.

When is research ethics committee review required in host and sponsor countries? Mtande and colleagues point out that many CRTs conducted in low- and middle-income countries are sponsored by other, wealthier nations. Yet, they state,

“The Ottawa Statement is silent on the need for host country and sponsor country review when a CRT is conducted in a low-resource setting. Additional guidance on when a protocol must be submitted for sponsor country review is needed... For instance, if an investigator’s role is limited to protocol development or the analysis of study data, must approval from her institution be sought?” [29].

They contend that too many full board reviews add needless burdens to CRTs, so the number of full board reviews should be minimized. Although this issue is not specific to CRTs, the *Ottawa Statement* could explain when both host and sponsor country review in multinational CRTs is required.

Identifying research participants

Among the 21 articles that discussed the *Ottawa Statement’s* recommendations regarding identifying research participants, 3 gaps were identified.

When should professionals be considered research participants in a CRT? The *Ottawa Statement* provides four criteria that can be used to identify who are the research participants in a CRT [6]. Mtande and colleagues apply these criteria to a case study to show that “when health workers merely *deliver* the study intervention, they are not research participants; when they are the *intended recipients* of the intervention, however, they are research participants.” [29]. But they contend that “difficult cases lie in the middle,” [29] and question whether training professionals to deliver an intervention confers participant status upon them. The *Ottawa Statement* could clarify the conditions under which professionals meet the definition of research participants.

Should professionals be offered less stringent protections when they are research participants in a CRT? According to van der Graaf and colleagues, when health providers are research participants in CRTs, they are “not

morally equivalent to ordinary research [participants]” as they have a different moral status [30]. This is because “their interests are protected... by professional codes of conduct.” [31]. As a result, professionals are owed less stringent protections than other research participants; for instance, they “should not be able to [decline or] withdraw easily when approached to participate in trials that aim to improve the health and well-being of patients.” [31].

Weijer and Taljaard caution that less stringent protections may not be justifiable for professionals, claiming that “all people possess a right to be free of medical or scientific experimentation without informed consent. This applies no less to health providers than patients in cluster randomized trials [even when research participation is] in line with [their] duties as employees.” [32]. To think otherwise “ignores the harms that may accrue to employees in research, including the revelation of substandard performance or reputational harms.” [32]. The *Ottawa Statement* could clarify the level of protection to which professionals are entitled when they are research participants in CRTs.

Who are ‘research bystanders’ in a CRT? In some CRTs, there are identifiable individuals or groups who do not meet the *Ottawa Statement’s* definition of research participants but who may nonetheless be substantially impacted by research. For example, in field trials of mosquito-borne diseases such as the EVITA Dengue trial [33], those who “undergo annual serologic surveillance for arboviral infection” meet one of the *Ottawa Statement’s* criteria of a research participant, i.e., “individuals who provide data by interacting with investigators.” [6]. However, people who are incidentally affected by the release of mosquitoes in the CRT do not meet any criterion of a research participants, since they are not the intended recipients nor directly targeted by an intervention. Since these individuals are not research participants, there is no obvious mechanism by which to offer them research protections.

Kimmelman refers to these individuals as research bystanders, and argues that, although few research guidelines or policies directly address protecting them, they are entitled to protections [34]. He states,

“A key task for research ethics is to safeguard the integrity of human research... [and that this entails] establishing and policing rules that stabilize the relationships that are necessary to sustain the research enterprise. [Since] some harms to bystanders can destabilize the types of collaboration necessary for a productive research enterprise... research ethics should consider and protect the welfare of bystanders.” [34].

The *Ottawa Statement* could provide a clear definition of research bystanders and outline what protections, if any, they are owed in CRTs.

Obtaining informed consent

Among the 37 articles that discussed the *Ottawa Statement's* recommendations regarding obtaining informed consent, 4 gaps were identified.

When should a CRT be considered minimal risk and infeasible to conduct with informed consent? According to the *Ottawa Statement*, a research ethics committee may approve an alteration or waiver of consent requirements when “(1) the research is not feasible without a waiver or alteration of consent, and (2) the study interventions and data collection procedures pose no more than minimal risk.” [6]. The *Ottawa Statement* explains that “minimal risk refers to the risks of daily life” while “feasibility will depend on a variety of factors including cluster size, proximity of cluster members (and thus ease of contact), complexity of the consent process, research infrastructure (such as number of local health workers available to approach cluster members), and research funding.” [6].

However, Choko and colleagues believe the *Ottawa Statement* should further clarify the conditions under which research participation should be considered minimal risk, and what could plausibly render a CRT infeasible if consent is required [30]. Consider that Selby and Krumholz believe “requiring individual informed consent may render important, low-risk studies impossible, especially in the case of large cluster randomized trials” as this kind of “research depends particularly on the full or nearly full participation of the study population.” [35]. The *Ottawa Statement* could provide additional details on when the criteria justifying alterations or waivers of consent requirements are met in CRTs.

When is using an opt-out strategy for recruitment appropriate in CRTs? Rogers and colleagues state that people “should never be forced into research participation, but, for [CRTs] comparing currently accepted standards of care, it may be appropriate that patients simply be informed that research is taking place and be given the right to withdraw from the intervention or from data collection (or both).” [22]. Anderson and colleagues agree, stating:

“While participants’ rights and interests must be respected, upholding such obligations may be possible using alternatives of notification and authorization to conventional informed consent procedures,

such as informing participants of the study and giving them the ability to opt out without penalty.” [36].

The *Ottawa Statement* could provide guidance on when opt-out approaches to consent are justified in CRTs.

What alternative consent approaches should be considered in CRTs? Symons and colleagues seek guidance on which alternative approaches of consent (e.g., electronic, integrated, short form consent) should be considered when an alteration of consent requirements is approved and, furthermore, on the precise form that alternative models should take in various circumstances [37]. Goldstein and colleagues add that “further work is required to evaluate the efficiency and acceptability of alternative approaches to informed consent, both in terms of recruitment and cost.” [21]. The *Ottawa Statement* could clarify the types of alternative consent approaches currently used in CRTs that may be appropriate.

When is assent required in a CRT? McPherson and colleagues argue that “cluster [trials] in the health sciences generally have less rigorous or even no direct engagement with assent procedures, which is in contrast to the range of alternate processes being developed for standard [randomized trials].” [38]. The *Ottawa Statement* could provide guidance on when assent (i.e., agreement from someone who is legally unable to consent due to limited or impaired decision-making capacity) is required in CRTs involving people who lack the capacity to provide informed consent.

Gatekeepers

Among the 14 articles that discussed the *Ottawa Statement's* recommendations regarding gatekeepers, 3 gaps were identified.

When can gatekeepers withhold permission for cluster enrolment? The *Ottawa Statement* recommends that gatekeeper permission be obtained for cluster enrolment. Sugarman and Califf point out that “gatekeepers can enhance or forestall the possibility of conducting research. For example, health system administrators may be opposed to research that might demonstrate a weakness in their delivery systems.” [39]. Federico and colleagues also worry about gatekeepers refusing to allow their community to participate in a CRT because of a conflict of interest; they state,

“As gatekeepers have interests that may not coincide with those of a learning health system, they have the ability to thwart research that could potentially improve health outcomes.” [9].

The *Ottawa Statement* could clarify the circumstances under which gatekeepers may justifiably withhold permission for the enrolment of clusters into a CRT.

Should language around consultation be updated? According to the *Ottawa Statement*, gatekeepers are often able to facilitate consultation activities. Mtande and colleagues suggest that the *Ottawa Statement* take on the language of “community engagement,” as this term is broader, encompassing “community involvement, consultation, and partnership.” [29]. The *Ottawa Statement* could update language around consultation to recognize the different levels of engagement activities from consultation (i.e., giving advice or feedback) through to decision making (i.e., collaboration and co-production) [40].

When should gatekeepers be engaged? Mtande and colleagues argue that “more guidance is needed on the timing of gatekeeper engagement. Practically, the trial may need to be funded before extensive engagement can occur. Furthermore, gatekeeper involvement may differ in protocol design, enrolment, implementation or reporting.” [29] The *Ottawa Statement* could provide more detail on which gatekeepers should be engaged, and when, during the different phases of a CRT.

Assessing benefits and harms

Among the 20 articles that discussed the *Ottawa Statement*'s recommendations regarding assessing benefits and harms, 6 gaps were identified.

How does equipoise apply to CRTs of health policy interventions? According to Horn and colleagues, the “application of equipoise to policy CRTs... seems to lead to solutions that are at once too restrictive and too permissive.” [41]. This is because one might believe that once a policy has been implemented, “it becomes the standard of care and depriving individuals of the protection of the policy violates equipoise. However, this position would undermine our ability to study existing policies that lack sound support and would hinder the development of evidence-based policy.” [41]. Alternatively, one might believe that the implementation of a policy that lacks sound support is consistent with equipoise. But “then it appears that the conduct of almost any CRT involving policy interventions is ethically permissible, even in cases in which policies clearly protect people from substantial risks.” [41]. The *Ottawa Statement* could clarify how to apply the concept of equipoise to CRTs involving health policy interventions.

How does equipoise apply to implementation research? According to Macklin, the *Ottawa Statement* fails to “make a clear distinction between CRTs that are [implementation research] and those that study an experimental intervention,” which is problematic because it confuses “two types of research: one in which the efficacy of a new intervention is being tested, and the second in which the implementation of an intervention with proven efficacy is being studied.” [42]. This confusion makes it possible for researchers to claim that clinical equipoise obtains. However, according to Macklin, “when the intervention arm is studying implementation of [an intervention proven to be effective elsewhere] and control facilities or units are observed but receive no intervention, the ethical question is the same as that in placebo-controlled RCTs. Is it ethical to withhold a proven intervention from a resource-poor community in the design of implementation CRTs?” [42]. The *Ottawa Statement* could clarify how to apply the concept of equipoise to CRTs constituting implementation research.

What level of care should be afforded to participants in the control arm of CRTs? Determining the appropriate level of care that should be afforded to participants in the control arm of CRTs is difficult. According to Choko and colleagues, this problem is especially pressing in CRTs conducted in low- and middle-income countries because, in these settings, it is not clear whether “those in the control arm [should] receive augmented care, care as defined by national (or even international) standards, or locally available care” [19].

They state,

“The issue of locally available care versus care mandated by national or international standards is an especially pressing issue in CRTs of implementation interventions. In order to obtain evidence that an intervention will improve care at the local level, locally available care is needed as the comparator group.” [19].

The *Ottawa Statement* could clarify the level of care that should be afforded to participants in the control arm of CRTs.

When is posttrial access to study interventions required in CRTs? Wagman and colleagues raise “the question of posttrial access to effective interventions, or study benefits more broadly” as it “continues to present challenges with respect to what interventions ought to be continued, for how long, and by whom” in CRTs, particularly those in low-resource settings where “expansion would not be feasible without additional investment beyond what has

been budgeted for in the evaluation.” [20]. The *Ottawa Statement* could provide guidance on the ethical imperative to provide posttrial access to study interventions.

When should CRTs have a Data and Safety Monitoring Committee? According to Anderson and colleagues, when “CRTs test the effectiveness of medical products or strategies in a manner that could result in major differences in morbid and mortal outcomes... it would be prudent to have a mechanism such as data monitoring committees.” [36]. The *Ottawa Statement* could clarify when a Data and Safety Monitoring Committee would be beneficial in CRTs and what should be under their purview.

When are interim analyses, stopping rules, and de-implementation strategies required? Doussau and Grady claim that when a stepped-wedge design is used “for experimental drugs or vaccines, interim analysis and stopping rules for efficacy, safety and futility might be necessary.” [43]. They propose that “case-specific simulation studies and analysis of the advantages and disadvantages of the [stepped-wedge] design may be necessary to appropriately evaluate the trade-offs in the choice between designs.” [43]. The *Ottawa Statement* could include discussion of interim analyses, stopping rules, and the de-implementation of interventions rolled out through stepped-wedge CRTs.

Protecting vulnerable participants

Among the 7 articles that discussed the *Ottawa Statement's* recommendations regarding protecting vulnerable participants, 1 gap was identified.

How should vulnerability be defined? The *Ottawa Statement* currently defines vulnerable research participants in terms of group membership. Mtande and colleagues argue that the *Ottawa Statement* should adopt a new definition that aligns with recent work on the concept [29]. For instance, vulnerability is defined in international ethics guidelines as individuals who “may have an increased likelihood of being wronged or incurring additional harm.” Rather than labelling groups as vulnerable, Mtande and colleagues suggest focusing on individual characteristics and contextual factors that may confer vulnerability status [29], which may include having limited decision-making capacity, being in a hierarchical relationship, being institutionalized, and having limited access to social goods.

Other

Among the 10 articles that discussed an issue outside the scope of an *Ottawa Statement* domain, 1 gap was identified.

How should issues related to equity, diversity, and inclusion be addressed in CRTs? Dowdy and colleagues argue that the generalizability of results from “CRTs evaluating the health impact of new diagnostic tests, especially in resource-limited settings... depends highly on geographic setting (e.g., ambient temperature and humidity), disease prevalence, and health system factors... It is therefore not sufficient to demonstrate the efficacy of a diagnostic test in a single setting.” [44]. If CRTs are not carried out in multiple settings and do not include diverse populations, there would be an “absence of comparative evidence on health impact from both centralized and peripheral levels.” [44]. As a result, Dowdy and colleagues state,

“Local policy makers could either restrict implementation to tertiary facilities where laboratory-based accuracy data can best be replicated or decentralize implementation without a proven health benefit. Restricting implementation to centralized facilities runs the risk of excluding disadvantaged populations from possible benefit, while decentralized implementation runs the risk of diverting scarce resources designated for the poor without improving their health. In either event, the poor and disadvantaged would be disproportionately affected.” [44].

The *Ottawa Statement* could include a new domain with recommendations that provide guidance on equity-related issues in CRTs, particularly those conducted in low-resource settings.

Discussion

Our findings identified 24 gaps with the *Ottawa Statement*. We found that issues with obtaining informed consent in CRTs are widely discussed in the literature citing the *Ottawa Statement*, whereas issues related to protecting vulnerable participants, gatekeepers, and research ethics committee review are discussed much less often. However, the number of times an issue is discussed does not necessarily reflect its importance. Each gap should be considered during the *Ottawa Statement* update process, but it will need to be determined whether the issue can be addressed with a new or revised recommendation or whether the issue is outside the scope of the *Ottawa Statement*. For instance, some of the identified gaps are about how to apply the existing *Ottawa Statement* recommendations to specific types of interventions; for example, how to apply the concept of equipoise to CRTs evaluating health policy or implementation interventions. As the *Ottawa Statement* recommendations are meant to be applicable to all CRTs, these types of gaps could be addressed after the *Ottawa Statement* is updated through the development of implementation guidance

documents similar to the implementation guidance document developed for CRTs in the hemodialysis [45]. Other gaps, such as the need for an updated definition of vulnerability, can also be addressed by appeal to more recently revised international ethics guidance documents [46, 47].

We also found that a substantial minority of the articles included in this citation analysis have a co-author who is also an author of the *Ottawa Statement*, its précis, or one of its background papers. This is due to our co-authors being highly productive members of the leading international team working on the ethics of CRTs. When relevant work is published in the ethics literature, our team regularly publishes articles and commentaries in response. Consequently, the identified gaps stem from productive engagement in the ethics literature, as opposed to a reflection of internal group discussions.

Finally, we found that the overwhelming majority of publications citing the *Ottawa Statement*, its précis, or one of its background papers had a first author affiliated with an institution from a high-income country. Considering these authors' pose (i.e., the standpoint from which they write) and gaze (i.e., who they write for) [48], some of the identified gaps may have nuances in low- and middle-income countries that are not discussed in the literature but which nonetheless require further guidance. For instance, recommending that researchers should provide posttrial access of study interventions to control clusters may be particularly challenging in resource-constrained settings. Engaging with researchers as well as patient and public partners from the Global South will be essential in the *Ottawa Statement* update process to ensure the *Ottawa Statement's* relevance to all CRTs.

Strengths and limitations

This review benefited from a robust methodological approach and an authorship group that includes ethicists, methodologists, social scientists, and trialists with expertise in CRTs, scoping reviews, and research ethics. However, we included only English-language publications. As CRT designs are increasingly used internationally, some articles addressing the *Ottawa Statement* recommendations or related ethical issues may have been overlooked. Additionally, because we included only articles that cited the *Ottawa Statement*, its précis, or one of its background papers, articles that discussed ethical issues in CRTs without citing these documents were not included. Finally, consistent with scoping review methodology, we did not assess article quality. While low-quality articles may have been included, there is currently no robust method to assess the quality of ethics articles.

Conclusion

Since the publication of the *Ottawa Statement*, there have been several developments in the landscape of research that demonstrate the need for an updated ethics guidance document. Our first step in the process of updating the *Ottawa Statement* was to conduct this citation analysis of articles that engage substantially with the *Ottawa Statement*, its précis, or its background papers to identify potential gaps. We identified 24 gaps that should be considered in the forthcoming *Ottawa Statement* update, alongside additional gaps identified in ongoing empirical work (e.g., systematic reviews of CRTs), through engagement with our patient and public partners, and through feedback from other content experts. As a next step to determine whether an identified gap will be addressed in the updated *Ottawa Statement*, a rapid review of the relevant literature will be required to sort identified gaps into four categories: (1) issue for which an ethical analysis has been completed and consensus on a new or revised recommendation is likely; (2) issue for which the ethical analysis is incomplete or consensus is unlikely, requiring completion of the ethical analysis with new or revised recommendation options including the advantages and disadvantages of each; (3) new issue, requiring an ethical analysis and new recommendation; and (4) issue outside of the scope of the *Ottawa Statement*. Ethical analyses of identified issues will run concurrently with empirical studies, the results of which will be shared as background materials to a working group tasked with updating the *Ottawa Statement*.

Abbreviation

CRT Cluster randomized trial

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

CEG, CW, JdT, MT, and NBM conceived of the project. JFS, KC, MT, and SGN undertook the initial screening for eligibility. CW and NBM completed the full-text review for eligibility. CEG, CW, JdT, and NBM developed the extraction form, and completed data extraction and qualitative analysis. CEG, JdT and NBM wrote the first draft of the manuscript with input from CW and MT. CEG was responsible for revisions of subsequent drafts. AB, AJL, BG, CW, EL, FA, JB, JdT, KG, KH, LGH, LM, MJ, MS, MT, NBM, PT, RAF, RvdG, SE, SLM, ST, SYHK, VAW provided feedback on subsequent drafts, had full access to all data and approved the decision to submit for publication. CEG is the guarantor of the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

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Competing interest

CW receives consulting income from Cardinal and Eli Lilly & Company. LGH's institution (RC2 NB) is supported by Foundation Clinical Neuroimmunology and Neuroscience Basel, and RC2 NB has a contract with Roche for a steering committee participation of LGH. All other authors declare no competing interests.

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