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Informed consent in cluster randomised trials: a guide for the perplexed

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ABSTRACT (193 words)

In a cluster randomised trial (CRT), intact social groups are randomised to the study intervention or control condition. The issue of informed consent in CRTs has been particularly challenging for researchers and research ethics committees. Some argue—incorrectly—that cluster randomisation is a reason not to seek informed consent from research participants. Systematic reviews have found that, relative to individually randomised trials, CRTs are associated with an increased likelihood of inadequate reporting of consent procedures and inappropriate use of waivers of consent. The objective of this paper is to provide a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs. We explicate a three-step framework for thinking through informed consent in CRTs: (1) identify research participants, (2) identify the study element(s) to which participants are exposed, (3) determine if a waiver of consent is appropriate for each study element. We apply our framework to examples of CRTs of cluster-level, professional-level, and individual-level interventions, and provide key lessons on informed consent for each type of CRT. We conclude that it is the unit of intervention—not the unit of randomisation—that drives informed consent issues in CRTs.

INTRODUCTION

Cluster randomisation is an increasingly popular trial design.[1] In a cluster randomised trial (CRT), intact social groups—such as communities, hospitals, or primary care practices—are randomised to the study intervention or control condition.[2] While interventions may be delivered to clusters, professionals (e.g., physicians), or individuals (e.g., patients), outcomes are usually measured on individuals within the clusters (although they may be summarised at the cluster-level during the analysis).

CRTs are essential for the evaluation of public health, health system, and knowledge translation interventions delivered at the cluster-level. But CRTs can also be a useful design for evaluating individual-level interventions when there is a compelling reason not to use individual randomisation—such as contamination, the need to study indirect intervention effects, or logistical challenges. For example, the evaluation of behavioural interventions may be undermined if participants in different study arms interact; trials of vaccinations aim to evaluate indirect effects of vaccines; and trials of protocolized healthcare interventions may be logistically easier to implement using cluster randomisation. Cluster randomisation has also been used in pragmatic trials, which aim to inform health decisions, to facilitate the evaluation of interventions in real-world settings with potentially limited research infrastructure.

CRTs raise manifold issues that are not present in individually randomised trials. CRTs are statistically complex. For example, individuals in the same cluster are usually similar in known and unknown ways, which means that larger sample sizes and more complex statistical methods are required to obtain correct inferences. CRTs are also susceptible to selection bias because participants are often recruited after the allocation is known. Further, CRTs often evaluate complex, multi-component interventions that can be logistically challenging to implement.

CRTs also raise novel ethical questions.[3] While the moral status of individuals has been broadly discussed and codified, CRTs involve social groups, and the moral status of social groups is not well understood. When an intervention is delivered to a community, should consent be sought from each community member or a community representative? CRTs are complex, multilevel studies in which the units of randomisation, intervention, and data collection may differ. For example, a single CRT may randomise hospitals, intervene upon physicians, and collect data from patients. This can make it difficult to identify research participants in a CRT and, by extension, who is entitled to ethical protections. As most research ethics guidelines were written with individually randomised trials in mind, application of ethics guidelines to CRTs is challenging.

The *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials* is the first international ethics guideline specific to CRTs.[4] The *Ottawa Statement* guides researchers and research ethics committees through the ethical issues posed by CRTs. It includes 15 recommendations across seven domains of ethical issues: justifying the cluster randomised design; research ethics committee review; the identification of research participants; informed consent; the role of gatekeepers; the assessment of risks and benefits; and the protection of vulnerable research participants.[4] The *Ottawa Statement* has been broadly influential. Since its publication, the Council for International Organisation of Medical Sciences,[5] the U.S.

Secretary's Advisory Committee on Human Research Protections (SACHRP),[6] and the Canada Interagency Panel on Research Ethics [7] have published additional ethical guidance on CRTs that align with the *Ottawa Statement*.

The issue of informed consent in CRTs has been particularly challenging for researchers and research ethics committees. Because CRTs are multilevel and complex, it may be difficult to determine from whom and for which aspects of the trial informed consent is required.[8] Further, CRT study interventions are commonly delivered to healthcare professionals, and researchers and research ethics committees may neglect to identify healthcare professionals as research participants from whom consent may be required. Finally, it is commonly thought—incorrectly—that cluster randomisation is a reason not to seek informed consent from study participants.[9] In fact, relative to individual randomisation, cluster randomisation is associated with an increased likelihood of inadequate reporting of consent procedures and failing to obtain informed consent from participants (Zhang J, Nicholls SG, Carroll K, Nix HP, Goldstein CE, Hey SP, Brehaut JC, McLean PC, Weijer C, Fergusson DA, Taljaard M. 2021. manuscript under review).

The objective of this paper is to build upon the *Ottawa Statement* by providing a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs. Broadly, three questions must be answered to determine whether informed consent should be obtained from an individual in a CRT (Figure 1). First, are the individuals in question research participants? Second, if they are research participants, to what study element(s) are they exposed? And third, do the conditions for a waiver of consent obtain for each study element? We argue that when answering these questions, researchers and research ethics committees should understand that it is the unit of intervention—not randomisation—that determines what is appropriate.

In what follows, we review the *Ottawa Statement* guidelines on informed consent in CRTs. Then we discuss how researchers and research ethics committees should answer the three questions when considering CRTs of cluster-level interventions, professional-level interventions, and individual-level interventions. For each type of CRT, key lessons are provided (Table 1) and an example is discussed in detail. In reality, it is common for one CRT to evaluate interventions with multiple components at multiple levels. However, for simplicity in this educational paper, we consider CRTs that exclusively evaluate interventions at a single level.

Table 1. Key lessons on informed consent in CRTs

Level of intervention	Key lessons
Any (cluster-, professional-, and individual-level interventions)	Informed consent for the study intervention and data collection are separable and should correspond to the participant's involvement in the study. A useful heuristic is: "Get consent where you can."

	If consent is sought at the earliest opportunity and before exposure to study interventions or data collection procedures, informed consent for randomisation is not required. Issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation
Cluster-level intervention	Cluster-level interventions are delivered to the community, hospital, or social group as a whole and cannot be avoided by individual cluster members. When cluster members cannot avoid exposure to the intervention, refusal of consent is effectively meaningless. The use of a waiver of consent for a cluster-level intervention is appropriate provided the intervention poses only minimal risk. Generally, when data collection occurs at the individual-level, informed consent for data collection is required.
Professional-level intervention	Professional-level interventions are delivered to healthcare professionals and, therefore, they are research participants. When health professionals are research participants their informed consent should be obtained unless the conditions for a waiver of consent are met. Patients are not research participants in CRTs of professional-level interventions unless they are the recipient of the study intervention, interacted with for data collection, or their private information is used. If patients are research participants in CRTs of professional-level interventions, it is usually because their identifiable private information is collected. Consent for data collection may be required.
Individual-level intervention	Considerations of informed consent are similar in individually randomised trials and CRTs of individual-level interventions because they test the same kinds of interventions. If an individual-level intervention would not qualify for a waiver of consent in an individually randomised trial, the intervention should not receive a waiver of consent in a CRT. If consent would be sought for an intervention in clinical practice, as with a drug or vaccine, a waiver of consent is never appropriate for that intervention in a CRT.

THE *OTTAWA STATEMENT* GUIDANCE ON INFORMED CONSENT

According to the *Ottawa Statement*, researchers have an obligation to seek informed consent from research participants in CRTs, unless the conditions for a waiver of consent obtain.[4] However, it can be difficult to identify research participants in CRTs. The *Ottawa Statement* defines a research participant as any individual whose interests may be directly impacted by research procedures.[4] This includes any individual who in the context of research is intervened upon, or interacted with for data collection, or whose private data is used. Importantly, both healthcare professionals and patients may be research participants in CRTs.

The *Ottawa Statement* provides recommendations that govern informed consent in CRTs.[4] While informed consent is generally required from research participants, a study may qualify for a waiver of consent if (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.[4] These two criteria are consistent across regulatory documents and international research ethics guidelines.[5, 7, 10] In a CRT, obtaining consent may be infeasible when consent is logistically challenging, for example due to excessive cluster size, limited research infrastructure (e.g., in low- and middle-income countries), or when individuals cannot meaningfully decline participation.[4] The infeasibility criterion is essential because the need for informed consent is not merely—or even primarily—about risk. Informed consent is about respecting autonomy and preserving the trust of research participants and the public. Minimal risk refers to the risks of daily life for average, healthy individuals, including the risks of routine physical examinations or the review of medical records. The burden of proof is on researchers to demonstrate to the research ethics committee that a waiver of consent is appropriate.

Informed consent for the study intervention and data collection are separable and should correspond to the participant's involvement in the study. For example, if the physician is the recipient of the study intervention and the patient only has her identifiable health information collected, researchers should seek consent for the study intervention from the physician and consent for data collection from the patient. A useful heuristic is: "Get consent where you can." Separate assessments of the appropriateness of a waiver of consent should be conducted for each component of the consent process.

CRTS OF CLUSTER-LEVEL INTERVENTIONS

In CRTs that evaluate cluster-level interventions, both the unit of randomisation and the unit of intervention are at the level of the social group (e.g., community, hospital, or school). By definition, cluster-level interventions are delivered to the entire social group. They cannot be divided at the level of the individual and therefore require the use of a cluster randomised design. Examples of cluster-level interventions include anti-smoking media campaigns delivered to municipalities,[11] water treatments delivered to groups of households with a shared water supply,[12] and community physical activity programs delivered to rural villages.[13]

Consider the Devon Active Village Evaluation (DAVE) trial.[13] It is a stepped wedge CRT which sought to evaluate the effectiveness of community physical activity programs as a means to increase physical activity in rural villages with populations of 500-2000 people. The

cluster-level study intervention involved organising and advertising community sport events, including advertisements in local media (newspapers, radio, and newsletters) as well as "posters in the local sports centres and village halls."[13] Data on participation in physical activity were collected by sending a survey and a prepaid return envelope to a random sample of households in each village.

Cluster-level interventions often manipulate the physical or social environment in a cluster, making it practically impossible for cluster members to avoid. The unavoidability of cluster-level interventions renders the participant's refusal of consent meaningless, because her decision to decline the intervention cannot be respected.

In the DAVE trial, the intervention was designed to impact community members directly through participation in sporting events, and indirectly through changing beliefs and attitudes about the need for regular exercise. Therefore, all community members were research participants in the DAVE trial because they were intervened upon whether or not they participated in sporting events. Further, the intervention was practically impossible for community members to avoid. For this reason, according to the *Ottawa Statement*, this study could only proceed with a waiver of consent for the intervention. However, recall that a cluster-level intervention can only qualify for a waiver of consent if, at the very least, both of the *Ottawa Statement* criteria for waiver of consent obtain.

The use of a waiver of consent for cluster-level interventions is an expansion of its historical scope of application. The waiver of consent was originally designed for retrospective review of medical records and behavioural research. When medical records are reviewed for research purposes, it is considered infeasible to track down each participant to obtain consent for the use of their data; a waiver of consent is generally acceptable so long as adequate confidentiality protections are in place.[14] In behavioural research, a waiver or alteration of consent is required when knowledge of the study objective, hypothesis, or interventions would alter participant behaviour and confound the results; provided research participation poses only minimal risk, a waiver or alteration of consent may be granted.[14] In CRTs of cluster-level interventions, obtaining participant consent for the study intervention is infeasible for a different reason: cluster members have little or no choice but to be exposed to the intervention.

The infeasibility of seeking informed consent for cluster-level interventions has implications for the kinds of interventions that can ethically be tested in these CRTs. CRTs of cluster-level interventions may only commence with a waiver of consent and must therefore pose no more than minimal risk to participants. In the context of CRTs of cluster-level interventions, examples of minimal risk activities include routine public health or educational practices.[8]

In the DAVE trial, a waiver of consent for the study intervention is appropriate. As explained above, requiring consent would have made the study infeasible because the cluster-level intervention was unavoidable. We believe the study intervention also only posed minimal risk to participants. The study intervention involved exposing community members to advertisements, in the same way as they are exposed to advertisements in their daily lives. Further, community members were free to participate in scheduled events or not. Therefore, the DAVE trial study intervention fulfils the requirements for a waiver of consent.

Although CRTs of cluster-level interventions involve randomising and intervening at the cluster-level, data collection is typically conducted either through interacting with individual cluster members, or through accessing routinely collected databases. Generally, written informed consent is required for data collection procedures. According to the *Ottawa Statement*, if the conditions for a waiver or alternation of consent for data collection are met, the research ethics committee may approve other methods of obtaining informed consent, such as electronic consent or information sheets with questionnaires.

In the DAVE trial, data were collected by surveys that were mailed to a random sample of households in each region. One adult per household was asked to fill out the survey, which included questions about demographics, participation in physical activity, and attitudes towards physical activity. The survey was accompanied by a participant information sheet. "Recipients of the survey were made aware that their participation was voluntary; therefore informed consent was…[obtained] when participants returned a completed questionnaire".[13] Through this process, informed consent for data collection was obtained.

CRTS OF PROFESSIONAL-LEVEL INTERVENTIONS

In CRTs of professional-level interventions, study interventions are delivered to healthcare professionals to produce an effect on patients.[15] This type of trial is useful for evaluating knowledge translation or health service interventions. Examples of professional-level interventions include decision support algorithms delivered to physicians to assist with medication dosing,[16] training sessions delivered to nursing home staff to implement evidence-based nonpharmacological interventions for managing aggressive patient behaviour,[17] and an online audit and feedback system delivered to multidisciplinary cardiac rehabilitation teams to improve the quality and coordination of care provided to patients.[18]

Consider the CARDSS trial.[18] It is a CRT of a professional-level intervention in which multidisciplinary cardiac rehabilitation teams received feedback on their concordance with established treatment guidelines and patient outcomes. Cardiac rehabilitation teams may include cardiologists, dieticians, nurses, physical therapists, psychologists, rehabilitation physicians, and social workers. The study intervention involved asking healthcare professionals to input deidentified patient data, including the treatments prescribed to patients and patient health outcomes, into the CARDSS Online system. Healthcare professionals then received feedback on their prescribing behaviours and patient outcomes. The feedback included a written report and an in-person education session led by a researcher, in which healthcare professionals had the opportunity to reidentify patient data to discuss specific cases. Both individually and as a group, healthcare professionals had the option to create action plans to improve team concordance with guidelines.

Recall, according to the *Ottawa Statement*, research participants are people who are the recipient of the study intervention or control condition, who are interacted with for data collection, or whose identifiable private information is collected.[4] Healthcare professionals are research participants in CRTs of professional-level interventions because they are the recipient of the intervention. Since researchers have an obligation to obtain informed consent from all

research participants, informed consent must be sought from healthcare professionals unless the criteria for a waiver of consent obtain.

It may be difficult to distinguish between CRTs in which the intervention is *delivered to* healthcare professionals and CRTs in which the intervention is *delivered by* healthcare professionals. When the intervention is *delivered to* healthcare professionals, such as the CARDSS study, it is designed to alter the behaviour of the healthcare professionals. In these studies, healthcare professionals are research participants. In contrast, some CRTs use healthcare professionals merely to deliver the study intervention to participants. In these CRTs, healthcare professionals may receive some training from researchers to ensure that they are able to deliver the intervention to patients properly. Once the training is complete, the study intervention is *delivered by* healthcare professionals to patients. Because the study intervention is not *delivered to* healthcare professional in these CRTs, they are not research participants. Therefore, researchers are not obligated to obtain informed consent from the healthcare professionals.

In the CARDSS trial, all components of the intervention were *delivered to* the team of healthcare professionals as a whole. The written reports, education sessions, and involvement in the creation and implementation of action plans to improve concordance with guidelines may have impacted the interests of healthcare professionals. Therefore, healthcare professionals were research participants. As research participants, their informed consent should be sought unless the conditions for a waiver of consent obtain.

A waiver of consent for the intervention may be justifiable for healthcare professionals in the CARDSS trial. Obtaining their informed consent may have been infeasible because the intervention was delivered to the cardiac rehabilitation team as a whole; the intervention could not be divided among individual healthcare professionals. Part of the intervention included developing action plans to improve the quality of care provided by the team. Each cardiac rehabilitation team member was able to assign action plan items to any other team member. Further, the study intervention included education sessions in which recent action plans were collaboratively reviewed to improve team coordination and performance. This aspect of the intervention was delivered to the team as a whole, making it infeasible for an individual healthcare professional to refuse to consent to the intervention. For healthcare professionals, using the CARDSS Online system, receiving feedback, and creating an action plan pose minimal risk

Unlike healthcare professionals, patients may not be research participants in some CRTs of professional-level interventions. Patients are research participants if they are intervened upon, interacted with for data collection, or their identifiable private information is collected. Patients are commonly not research participants in CRTs evaluating professional-level knowledge translation interventions. Knowledge translation interventions that promote the uptake of evidence-based behaviours do not interfere with the physician's individualised judgement on behalf of her patient. Healthcare professionals are free to make treatment and diagnostic decisions in accord with their fiduciary duties to patients and, as a result, these interventions do not impact the medical interests of patients. Therefore, in this type of CRT of a professional-level intervention, patients are not intervened upon. Some knowledge translation trials measure patient outcomes using only routinely collected databases with patient identifiers removed. If a

patient is not intervened upon, not interacted with for data collection, and her identifiable private health information is not collected or accessed for the purposes of the study, she is not a research participant and her informed consent for research is not required. However, if one or more of these conditions obtain, patients qualify as research participants. In such cases, patient consent is required, unless conditions for a waiver of consent obtain. If patients are research participants in a CRT of a professional-level intervention, it is usually because data on their clinical outcomes are collected.

In the CARDSS trial, the intervention was not delivered to patients and did not interfere with the fiduciary duties of healthcare professionals. The intervention made healthcare professionals aware of inconsistencies between their clinical performance and established treatment guidelines. While this may have altered healthcare professionals' treatment decisions, they maintained the ability to tailor treatment to the needs of individual patients. As the physician's judgment on behalf of her patient was preserved, the patient's medical interests were not undermined by the study intervention. However, identifiable information was collected from patients in this trial. Healthcare professionals inputted deidentified patient data into the CARDSS Online System, and this deidentified data was sent to researchers. But the nature of the intervention required healthcare professionals in the trial to retain the ability to easily reidentify patient data. Therefore, patient data used in the CARDSS trial were identifiable. The use of patients' identifiable information may impact patients' interests because it places them at risk of invasions of privacy, breaches of confidentiality, and inappropriate use of their data. Therefore, patients were research participants in the CARDSS trial and their informed consent for data collection was required. Correctly, researchers obtained informed consent for data collection from patients.

CRTS OF INDIVIDUAL-LEVEL INTERVENTIONS

CRTs of individual-level interventions and individually randomised trials evaluate the same kinds of interventions. These interventions are delivered to patients and healthy volunteers. Examples of individual-level interventions include direct observed iron supplement therapy,[19] prescribed physical activity regimens,[20] and antibiotics.[21]

Consider the Prevention of Infections in Cardiac Surgery (PICS) trial.[21] It is a pragmatic CRT of an individual-level intervention that evaluated different combinations of commonly used antibiotics for the prevention of post-operative sternal surgical site infections. Patient outcomes were measured through routinely collected data and one phone call by research staff at least 90 days after surgery.

The identification of research participants is straight-forward in both individually randomised trials and CRTs of individual-level interventions because the same individual—commonly a patient—is exposed to the study intervention and the data collection procedures. In the PICS trial, patients are research participants because they were the recipient of the study intervention and they interacted with researchers for the purpose of data collection.

Considerations of informed consent are similar in individually randomised trials and CRTs of individual-level interventions because issues of consent are a function of the level of intervention, not the unit of randomisation. Both types of trials require similar justifications for a

waiver of consent. Individually randomised trials rarely meet the conditions for a waiver of consent.[22] The same is true of CRTs of individual-level interventions. Generally, the administration of an individual-level intervention, in either an individually randomised trial or a CRT, involves an encounter between healthcare professional and patient. Consequently, it is typically feasible to ask for informed consent for both the study intervention and data collection at this time. The feasibility of obtaining informed consent in trials of individual-level interventions means that waivers of consent are rarely appropriate.

One difference between individually randomised trials and CRTs, including CRTs of individual-level interventions, is that clusters in CRTs may need to be randomised before participants are recruited.[23, 24] This means that when potential participants are approached for recruitment, they cannot meaningfully decline randomisation. The function of informed consent is to allow prospective participants to adopt the ends of the study as their own before they are exposed to risk.[8] To satisfy this requirement, researchers should seek informed consent at the earliest opportunity, and before participants are exposed to the risks posed by study interventions or data collection procedures. Seeking consent from cluster members at the time of enrollment fulfills the requirements of respect for persons.[8]

As with individually randomised trials, waivers of consent in CRTs of individual-level interventions are rarely justifiable. A useful heuristic is: a waiver of consent for a CRT of an individual-level intervention should only be granted if an individually randomised trial testing the same intervention would also qualify for a waiver of consent.[25] In spite of their similarity to individually randomised trials, determining the appropriateness of waivers of consent for CRTs of individual-level interventions has been particularly challenging for research ethics committees.

Research ethics committees commonly approve waivers of consent for CRTs of individual-level interventions that do not fulfill the requirements for a waiver of consent.[26] In a systematic review of 40 CRTs of individual-level interventions, eight trials were granted a waiver of consent, but only one trial provided justifications for the waiver of consent that were consistent with regulatory criteria for a waiver of consent.[26] Illegitimately accepted justifications for waivers of consent included: the use of "usual care" study interventions; the pragmatic nature of the trial; and cluster randomisation.[26] The acceptance of these extraneous justifications creates a loophole in the ethical oversight of research.[25] Further, the illegitimate use of waivers of consent undermines the autonomy rights of participants and potentially exposes RECs and their institutions to legal liability and sanction by government authorities.

To address the pressing problem of illegitimate use of waivers of consent in CRTs of individual-level intervention, a list of potential justifications for a waiver of consent and suitable follow-up questions for research ethics committees to ask researchers are found in Table 2. This table is intended to equip research ethics committees with the tools they need to navigate applications for waivers of consent in CRTs of individual-level interventions.

Table 2. Questions for putative justifications for waiver of consent in CRTs of individual-level interventions

Justification	Follow-up question for researchers
Requiring informed consent would undermine the pragmatic goals of the study.	Why would obtaining informed consent be especially detrimental to the generalisability of the trial results? Is there reason to believe that many prospective participants, if asked, would be likely to refuse? Have any other measures been taken to secure buy-in and improve recruitment (e.g., through engagement with patients, patients' families, or community organisations)?
Requiring informed consent would exclude patients who require urgent care.	What proportion of surgeries/ medical care are emergency cases in the participating institutions? Can informed consent be obtained from all non-emergency cases and an emergency exception from informed consent be sought for all emergency cases?
Requiring informed consent would exclude potential participants who are not proficient in the official languages in the region.	How many patients are expected to be excluded for this reason? Why would their exclusion be detrimental to the generalisability of this study? Is it feasible to have a translator present for the consent process?
Obtaining informed consent is impracticable because surgical/ medical care is highly protocolized.	Are there any exclusion criteria for the intervention protocol when it is used in clinical care? Are there medical contraindications (e.g., drug allergy) to any aspect of protocolized care?
Obtaining informed consent is impracticable because it would be prohibitively expensive.	Is the excessive cost attributed to the use of cluster randomisation or due to the informed consent process? What would the required sample size have been under individual randomisation? Can more statistically efficient trial designs be used?

	Can more cost-efficient methods of obtaining consent be used? Can more cost-efficient methods of data collection be used?
Obtaining informed consent is unnecessary because patients do not normally decide which treatment regimen they receive.	In clinical practice, are treatments allocated systematically to generate knowledge that will benefit future patients? Is the treatment regimen normally allocated randomly? Are there known or likely substantial or materially relevant differences between the treatment regiments in side effects, efficacy or patient burden (e.g., frequency of administration, duration of treatment)?
The interventions are minimal risk because they are usual care.	Does participating in the trial impact the trajectory of care for individual patients? Are all of these care trajectory deviations minimal risk? Are the risks of adverse effects from the interventions similar to those experienced in the everyday life of healthy individuals?

The PICS trial illustrates many of the justifications for a waiver of consent that a research ethics committee may see and need to arbitrate in CRTs of individual-level interventions. In the PICS trial, researchers justified the need for a waiver of consent by arguing that obtaining informed consent would (1) undermine generalisability and pragmatism of the trial, (2) be impracticable because cardiac surgeries are protocolized, (3) be impracticable because of cost, (4) be unnecessary because the interventions fell within the standard of care and, thus, were minimal risk, and (5) be unnecessary because in clinical practice, patients do not normally decide which treatment regimen they receive.[21] Are these acceptable justifications for a waiver of consent?

Is generalisability an acceptable justification to waive informed consent? In every clinical trial, relevant differences may distinguish those who consent to participate in the trial from those who decline participation. Seeking informed consent may thereby decrease the applicability of trial results to the target population. Although promoting generalisability is especially relevant in designing pragmatic trials, the generalisability of a trial is not more important than respecting the autonomy of participants. The requirement for the informed consent of research participants is grounded in law, human rights, and self-determination.[27] It operationalises the principle of respect for persons and is a central protection in human research. If the generalisability of a study superseded the ethical principle of respect for persons, most—if not all—research with human participants could be conducted without informed consent. Generalisability is not an acceptable justification for a waiver of consent. Rather than avoiding consent, researchers should consider other means of improving recruitment, for example, through consulting with stakeholders (e.g., patients, patients' families, and community organisations) during protocol design.

When an individual-level intervention is implemented as a policy, is it feasible to obtain informed consent? Cluster-level interventions are delivered to intact social groups and are not divisible at the level of the individual, making it very difficult or impossible to obtain informed consent from participants. However, policies that prescribe individual-level interventions are not cluster-level interventions. Treatment policies contain medical exceptions for patients, for example excluding or offering an alternative treatment to patients with a history of allergy to the drug. This accommodation is possible because the intervention is divisible at the level of the individual. Like a medical contraindication, a patient's refusal of research participation should exclude her. The implementation of an individual-level intervention as a policy is not a valid justification for a waiver of consent.

Is obtaining informed consent infeasible if it is expensive? Obtaining informed consent increases the cost of every clinical trial. In some cases, the costs may be prohibitively high. For example, pragmatic trials usually seek to study interventions using cost-efficient designs. However, researchers are obligated to demonstrate this to the research ethics committee. When applying for a waiver of consent, researchers should justify the statistical and cost-efficiency of the trial design. CRTs are statistically inefficient, requiring a larger sample size than an analogous individually randomised trial; researchers should provide cost estimates for conducting an individually randomised trial in which informed consent is sought. Further, researchers should justify proposed informed consent and data collection procedures. These procedures substantially impact the costs of a trial and can often be optimised. For example, healthcare professionals, as opposed to hired research staff, may be used to obtain informed consent from patients to avoid excessive costs. Importantly, the cost of alterations of consent such as electronic consent, verbal consent, and shortened consent forms should be considered when applying for a waiver of consent.

Is obtaining informed consent unnecessary if patients do not normally decide which treatment regimen they receive in clinical practice? In clinical practice, there may be procedures for which informed consent is not usually obtained. For example, a patient is not typically consulted about the type of suture used to close a wound. However, the standard for informed consent in research is higher than in clinical practice.[28] Unlike clinical practice, research exposes individuals to risk at least in part for the benefit of others. Using an individual for the benefit of others heightens the need for informed consent to allow her to adopt the goals of the study as her own. Therefore, the fact that consent is not obtained for a procedure in clinical practice does not imply that consent need not be obtained in research.

Are interventions that fall within the standard of care minimal risk? At the population level, two interventions that fall within the standard of care may, on average, pose similar levels of risk to patients. However, for an individual patient, the risks of two treatments that fall within the standard of care may differ substantially.[29] For example, angiotensin converting enzyme (ACE) inhibitors and thiazide diuretics fall within the standard of care for high blood pressure, and they have similar risk profiles at the population level.[30] However, administering ACE inhibitors to pregnant patients can result in fetal harm, while administering thiazide diuretics can trigger gout attacks in patients with a history of the disease.[30]

In clinical trials, the processes of randomisation and treatment protocolization may alter the trajectory of care of individual patients. If the alteration results in a convergence of an individual risk factor with an intervention side effect, the intervention may pose more than minimal risk. If a subset of participants in the PICS trial are more susceptible to the side effects of the antibiotics (e.g., diarrhea or *Clostridium difficile* infections), and their care is altered because of the study, participating in the trial could pose more than minimal risk. For this reason, interventions that fall within the standard of care may well not be minimal risk when they are study interventions.

The PICS trial illustrates that it is difficult to justify a waiver of consent for individual-level interventions, regardless of the unit of randomisation. In the PICS trial, like all trials of individual-level interventions, the intervention is administered through an encounter with research participants. Informed consent for the study intervention and data collection can feasibly be obtained during this interaction. As with individually randomised trials, it is rarely appropriate for cluster randomised trials that involve a drug or vaccine intervention to be granted a waiver of consent.

TRANSLATING THE OTTAWA STATEMENT INTO NATIONAL REGULATORY CONTEXTS

The framework we have proposed in this paper is meant to help researchers and research ethics committees navigate issues of informed consent in CRTs. Our framework relies on the definition of a research participant and criteria for a waiver of consent that are outlined in the *Ottawa Statement*. National research regulations may differ in their definition of a research participant, and they may outline additional criteria for a waiver of consent. Therefore, additional work is required to translate our framework for application with various national research regulations.

Such translational work was done in the United States after the publication of the *Ottawa Statement.* SACHRP translated the *Ottawa Statement* recommendations to apply in the U.S. regulatory context.[6] SACHRP determined that many of the *Ottawa Statement* recommendations straightforwardly align with U.S. regulations, including the need to justify cluster randomisation, the role of gatekeepers, and the need to obtain informed consent from all research participants unless the criteria for a waiver of consent obtain. However, SACHRP noted several points of divergence between the *Ottawa Statement* recommendations and U.S. regulations. Each has a different definition of a research participant, and U.S. regulations specify several additional criteria for a waiver of consent. Additionally, if a study aims to evaluate an intervention that alters how healthcare professionals deliver care to patients, the *Ottawa Statement* would classify it as a CRT of a professional-level intervention. In contrast, SACHRP may classify the study as a quality improvement activity—not research—if the study meets certain criteria in U.S. guidance documents. Our purpose here to not to weigh in on these points of disagreement, but to illustrate how ethical guidelines can be translated to apply to existing regulations.

CONCLUSION

Issues of informed consent in CRTs are challenging for researchers and research ethics committees. This paper seeks to provide a framework for thinking through these challenges.

Issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation. We provide guidance over issues of informed consent that arise in CRTs of cluster-level, professional-level, and individual-level interventions. As the popularity of CRTs continues to increase, researchers and research ethics committees must ensure that CRTs are conducted in accordance with the principle of respect for persons and the rules governing informed consent.

CONTRIBUTORSHIP STATEMENT

HPN and CW led the development of the article and wrote the first draft. All other authors (JCB, DF, CEG, and MT) provided detailed comments and revisions on subsequent drafts of the paper. All authors approved the final version of the paper.

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Figure 1. A schematic representation of how researchers and research ethics committees should navigate issues of informed consent in CRTs.

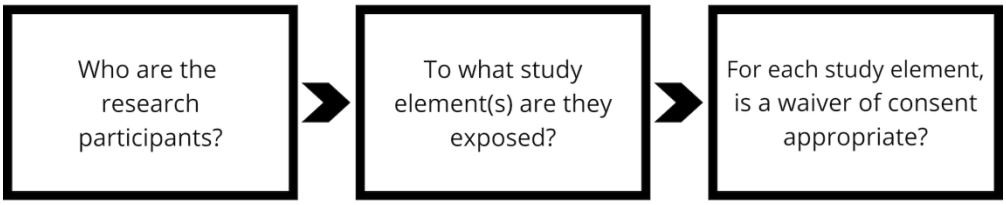

Figure 1. A schematic representation of how researchers and research ethics committees should navigate issues of informed consent in CRTs.

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ABSTRACT (193 words)

In a cluster randomised trial (CRT), intact groups—such as communities, clinics, or schools—are randomised to the study intervention or control conditions. The issue of informed consent in CRTs has been particularly challenging for researchers and research ethics committees. Some argue that cluster randomisation is a reason not to seek informed consent from research participants. In fact, systematic reviews have found that, relative to individually randomised trials, CRTs are associated with an increased likelihood of inadequate reporting of consent procedures and inappropriate use of waivers of consent. The objective of this paper is to clarify this confusion by providing a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs. In CRTs, it is the unit of intervention—not the unit of randomisation—that drives informed consent issues. We explicate a three-step framework for thinking through informed consent in CRTs: (1) identify research participants, (2) identify the study element(s) to which participants are exposed, (3) determine if a waiver of consent is appropriate for each study element. We then apply our framework to examples of CRTs of cluster-level, professional-level, and individual-level interventions, and provide key lessons on informed consent for each type of CRT.

INTRODUCTION

Cluster randomisation is an increasingly popular trial design.[1] In a cluster randomised trial (CRT), intact groups or "clusters" of people—such as communities, hospitals, or primary care practices—are randomised to the study intervention or control condition.[2] While interventions may be delivered to the entire cluster, to professionals (e.g., physicians) within each cluster, or directly to individual patients, outcomes are usually measured on multiple individuals within each cluster (although they may be summarised at the cluster-level during the analysis).

CRTs are essential for the evaluation of public health, health system, and knowledge translation interventions delivered at the cluster-level. But CRTs can also be a useful design for evaluating individual-level interventions when there is a compelling reason not to use individual randomisation—such as contamination, the need to study indirect intervention effects, or logistical challenges. For example, the evaluation of behavioural interventions may be undermined if participants in different study arms interact; trials of vaccinations aim to evaluate indirect effects of vaccines; and interventions of protocolized treatments, such as intravenous fluid resuscitation, may be logistically easier to deliver to patients using cluster randomisation. Cluster randomisation has also been used in pragmatic trials, which aim to inform health decisions, to facilitate the evaluation of interventions in real-world settings with potentially limited research infrastructure. However, avoiding the need to seek informed consent is an inappropriate justification for adopting a cluster randomised design.

CRTs raise manifold issues that are not present in individually randomised trials. CRTs are statistically complex. For example, individuals in the same cluster are usually similar in known and unknown ways, which means that larger sample sizes and more complex statistical methods are required to obtain correct inferences. CRTs are also susceptible to selection bias because participants are often recruited after the allocation is known. Further, CRTs often evaluate complex, multi-component interventions that can be logistically challenging to implement.

CRTs also raise novel ethical questions.[3] While the rights and interests of individuals have been broadly discussed and codified, CRTs involve intact groups, and the rights and of groups are not well understood. When an intervention is delivered to a community, should consent be sought from each community member or a community representative? CRTs are complex, multilevel studies in which the units of randomisation, intervention, and data collection may differ. For example, a single CRT may randomise hospitals, intervene upon physicians, and collect data from patients. This can make it difficult to identify research participants in a CRT and, by extension, who is entitled to ethical protections. As most research ethics guidelines were written with individually randomised trials in mind, application of ethics guidelines to CRTs is challenging.

The *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials* is the first international ethics guideline specific to CRTs.[4] The *Ottawa Statement* guides researchers and research ethics committees through the ethical issues posed by CRTs. It includes 15 recommendations across seven domains of ethical issues: justifying the cluster randomised design; research ethics committee review; the identification of research participants; informed

consent; the role of gatekeepers; the assessment of risks and benefits; and the protection of vulnerable research participants.[4] The *Ottawa Statement* has been broadly influential. Since its publication, the Council for International Organisation of Medical Sciences,[5] the United States (US) Secretary's Advisory Committee on Human Research Protections (SACHRP),[6] and the Canada Interagency Panel on Research Ethics have published additional ethical guidance on CRTs that align with the *Ottawa Statement*.[7]

The issue of informed consent in CRTs has been particularly challenging for researchers and research ethics committees. Because CRTs are multilevel and complex, it may be difficult to determine from whom and for which aspects of the trial informed consent is required.[8] Further, CRT study interventions are commonly delivered to healthcare professionals, and researchers and research ethics committees may neglect to identify healthcare professionals as research participants from whom consent may be required. Finally, it is commonly thought that cluster randomisation is a reason not to seek informed consent from study participants.[9] In fact, relative to individual randomisation, cluster randomisation is associated with an increased likelihood of inadequate reporting of consent procedures and failing to obtain informed consent from participants (Zhang J, Nicholls SG, Carroll K, Nix HP, Goldstein CE, Hey SP, Brehaut JC, McLean PC, Weijer C, Fergusson DA, Taljaard M. 2021. manuscript under review).

The objective of this paper is to build upon the *Ottawa Statement* by providing a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs. We argue that it is the unit of intervention—not randomisation—that drives issues of informed consent in CRTs. We offer a three-step framework to determine whether informed consent should be obtained from an individual in a CRT (Figure 1). First, are the individuals in question research participants? Second, if they are research participants, to what study element(s) are they exposed? And third, do the conditions for a waiver of consent obtain for each study element? In what follows, we review the *Ottawa Statement* guidelines on informed consent in CRTs. Then we apply our three-step framework to CRTs of cluster-level interventions, professional-level interventions, and individual-level interventions. For each type of CRT, key lessons are provided (Table 1) and an example is discussed in detail. In reality, it is common for one CRT to evaluate interventions with multiple components at multiple levels. However, for simplicity in this educational paper, we consider CRTs that exclusively evaluate interventions at a single level. When dealing with complex CRTs, the three-step framework presented here should be used to evaluate each study intervention and data collection procedure separately.

Table 1. Key lessons on informed consent in CRTs

Level of intervention	Key lessons
Any (cluster-, professional-, and	Informed consent for the study intervention and data collection are separable and should correspond to the participant's involvement in the study. A useful heuristic is: "Get consent where you can."

individual-level interventions)	If consent is sought at the earliest opportunity and before exposure to study interventions or data collection procedures, informed consent for randomisation is not required. Issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation
Cluster-level intervention	Cluster-level interventions are delivered to the community, hospital, or social group as a whole and cannot be avoided by individual cluster members. When cluster members cannot avoid exposure to the intervention, refusal of consent is effectively meaningless. The use of a waiver of consent for cluster-level interventions is appropriate provided the intervention poses only minimal risk. Generally, when data collection occurs at the individual-level, informed consent for data collection is required.
Professional-level intervention	Professional-level interventions are delivered to healthcare professionals and, therefore, they are research participants. When health professionals are research participants their informed consent should be obtained unless the conditions for a waiver of consent are met. Patients are not research participants in CRTs of professional-level interventions unless they are the recipient of the study intervention, interacted with for data collection, or their private information is used. If patients are research participants in CRTs of professional-level interventions, it is usually because their identifiable private information is collected. Consent for data collection may be required.
Individual-level intervention	Considerations of informed consent are similar in individually randomised trials and CRTs of individual-level interventions because they test the same kinds of interventions. If an individual-level intervention would not qualify for a waiver of consent in an individually randomised trial, the intervention should not receive a waiver of consent in a CRT. If consent would be sought for an intervention in clinical practice, as with a drug or vaccine, a waiver of consent is never appropriate for that intervention in a CRT.

THE *OTTAWA STATEMENT* GUIDANCE ON INFORMED CONSENT

According to the *Ottawa Statement*, researchers have an obligation to seek informed consent from research participants in CRTs, unless the conditions for a waiver of consent obtain.[4] However, it can be difficult to identify research participants in CRTs. The *Ottawa Statement* defines a research participant as any individual whose interests may be directly impacted by research procedures.[4] This includes any individual who in the context of research is intervened upon, or interacted with for data collection, or whose private data is used. Importantly, both healthcare professionals and patients may be research participants in CRTs.

The *Ottawa Statement* provides recommendations that govern informed consent in CRTs.[4] While informed consent is generally required from research participants, a study may qualify for a waiver of consent if (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.[4] These two criteria are consistent across regulatory documents and international research ethics guidelines.[5, 7, 10] In a CRT, obtaining consent may be infeasible when individuals cannot meaningfully decline participation.[4] The infeasibility criterion is essential because the need for informed consent is not merely—or even primarily—about risk. Informed consent is about respecting autonomy and preserving the trust of research participants and the public. Minimal risk refers to the risks of daily life for average, healthy individuals, including the risks of routine physical examinations or the review of medical records. The burden of proof is on researchers to demonstrate to the research ethics committee that a waiver of consent is appropriate.

Informed consent for the study intervention and data collection are separable and should correspond to the participant's involvement in the study. For example, if the physician is the recipient of the study intervention and the patient only has her identifiable health information collected, researchers should seek consent for the study intervention from the physician and consent for data collection from the patient. A useful heuristic is: "Get consent where you can." Separate assessments of the appropriateness of a waiver of consent should be conducted for each component of the consent process.

CRTS OF CLUSTER-LEVEL INTERVENTIONS

In CRTs that evaluate cluster-level interventions, both the unit of randomisation and the unit of intervention are at the level of the social group (e.g., community, hospital, or school). By definition, cluster-level interventions are delivered to the entire social group. They cannot be divided at the level of the individual and therefore require the use of a cluster randomised design. Examples of cluster-level interventions include anti-smoking media campaigns delivered to municipalities,[11] water treatments delivered to groups of households with a shared water supply,[12] and community physical activity programs delivered to rural villages.[13]

Consider the Devon Active Village Evaluation (DAVE) trial.[13] It is a stepped wedge CRT which sought to evaluate the effectiveness of community physical activity programs as a means to increase physical activity in rural villages with populations of 500-2000 people. The cluster-level study intervention involved organising and advertising community sport events,

including advertisements in local media (newspapers, radio, and newsletters) as well as "posters in the local sports centres and village halls."[13] Data on participation in physical activity were collected by sending a survey and a prepaid return envelope to a random sample of households in each village.

Cluster-level interventions often manipulate the physical or social environment in a cluster, making it practically impossible for cluster members to avoid. The unavoidability of cluster-level interventions renders the participant's refusal of consent meaningless, because her decision to decline the intervention cannot be respected.

In the DAVE trial, the intervention was designed to impact community members directly through participation in sporting events, and indirectly through changing beliefs and attitudes about the need for regular exercise. Therefore, all community members were research participants in the DAVE trial because they were intervened upon whether or not they participated in sporting events. Further, the intervention was practically impossible for community members to avoid. For this reason, according to the *Ottawa Statement*, this study could only proceed with a waiver of consent for the intervention. However, recall that a cluster-level intervention can only qualify for a waiver of consent if, at the very least, both of the *Ottawa Statement* criteria for waiver of consent obtain.

The use of a waiver of consent for cluster-level interventions is an expansion of its historical scope of application. The waiver of consent was originally designed for retrospective review of medical records and behavioural research. Originally, it did not encompass randomised trials. Its scope was limited to retrospective medical record reviews and behavioural research: two types of non-randomised studies. When medical records are reviewed for research purposes outside of randomised trials, it is considered infeasible to track down each participant to obtain consent for the use of their data; a waiver of consent is generally acceptable so long as adequate confidentiality protections are in place.[14] In behavioural research, a waiver or alteration of consent is required when knowledge of the study hypothesis or interventions would alter participant behaviour and confound the results; provided research participation poses only minimal risk, a waiver or alteration of consent may be granted.[14] The *Ottawa Statement* expanded the scope of the infeasibility criterion for a waiver of consent to encompass cluster-level interventions in CRTs, in which cluster members have little or no choice but to be exposed to the intervention.

The infeasibility of seeking informed consent for cluster-level interventions has implications for the kinds of interventions that can ethically be tested in these CRTs. CRTs of cluster-level interventions may only commence with a waiver of consent and must therefore pose no more than minimal risk to participants. In the context of CRTs of cluster-level interventions, examples of minimal risk activities include routine public health or educational practices.[8]

In the DAVE trial, a waiver of consent for the study intervention is appropriate. As explained above, requiring consent would have made the study infeasible because the cluster-level intervention was unavoidable. We believe the study intervention also only posed minimal risk to participants. The study intervention involved exposing community members to advertisements, in the same way as they are exposed to advertisements in their daily lives.

Further, community members were free to participate in scheduled events or not. Therefore, the DAVE trial study intervention fulfils the requirements for a waiver of consent.

Although CRTs of cluster-level interventions involve randomising and intervening at the cluster-level, data collection is typically conducted either through interacting with individual cluster members, or through accessing routinely collected databases. Generally, written informed consent is required for data collection procedures. According to the *Ottawa Statement*, if the conditions for a waiver or alteration of consent for data collection are met, the research ethics committee may approve other methods of obtaining informed consent, such as electronic consent or information sheets with questionnaires.

In the DAVE trial, data were collected by surveys that were mailed to a random sample of households in each region. One adult per household was asked to fill out the survey, which included questions about demographics, participation in physical activity, and attitudes towards physical activity. The survey was accompanied by a participant information sheet. "Recipients of the survey were made aware that their participation was voluntary; therefore informed consent was…[obtained] when participants returned a completed questionnaire".[13] Through this process, informed consent for data collection was obtained.

CRTS OF PROFESSIONAL-LEVEL INTERVENTIONS

In CRTs of professional-level interventions, study interventions are delivered to healthcare professionals to produce an effect on patients.[15] This type of trial is useful for evaluating knowledge translation or health service interventions. Examples of professional-level interventions include decision support algorithms delivered to physicians to assist with medication dosing,[16] training sessions delivered to nursing home staff to implement evidence-based nonpharmacological interventions for managing aggressive patient behaviour,[17] and an online audit and feedback system delivered to multidisciplinary cardiac rehabilitation teams to improve the quality and coordination of care provided to patients.[18]

Consider the CARDSS trial.[18] It is a CRT of a professional-level intervention in which multidisciplinary cardiac rehabilitation teams received feedback on their concordance with established treatment guidelines and patient outcomes. Cardiac rehabilitation teams may include cardiologists, physical therapists, nurses, psychologists, dieticians, social workers, and rehabilitation physicians. The study intervention involved asking healthcare professionals to input deidentified patient data, including the treatments prescribed to patients and patient health outcomes, into the CARDSS Online system. Healthcare professionals then received feedback on their prescribing behaviours and patient outcomes. The feedback included a written report and an in-person education session led by a researcher. Importantly, during the education session, healthcare professionals were given the opportunity to reidentify patient data to discuss the details of specific cases. Both individually and as a group, healthcare professionals had the option to create action plans to improve team concordance with guidelines.

Recall that, according to the *Ottawa Statement*, research participants are people who are the recipient of the study intervention or control condition, who are interacted with for data collection, or whose identifiable private information is collected.[4] Healthcare professionals are research participants in CRTs of professional-level interventions because they are the recipient of

the intervention. Since researchers have an obligation to obtain informed consent from all research participants, informed consent must be sought from healthcare professionals unless the criteria for a waiver of consent obtain.

It may be difficult to distinguish between CRTs in which the intervention is *delivered to* healthcare professionals and CRTs in which the intervention is *delivered by* healthcare professionals. When the intervention is *delivered to* healthcare professionals, such as the CARDSS study, it is designed to alter the behaviour of the healthcare professionals. In these studies, healthcare professionals are research participants.

In contrast, some CRTs use healthcare professionals merely to deliver the study intervention to participants. In these CRTs, healthcare professionals may receive some training from researchers to ensure that they are able to deliver the intervention to patients properly. Once the training is complete, the study intervention is *delivered by* healthcare professionals to patients. Because the study intervention is not *delivered to* healthcare professional in these CRTs, they are not research participants. Therefore, researchers are not obligated to obtain informed consent from the healthcare professionals. For example, the REMCARE trial evaluated the effectiveness of group reminiscence therapy for people living with dementia and their family caregivers.[19] Researchers trained healthcare professionals to facilitate the group therapy sessions. The primary objective of the trial was to evaluate the effectiveness of the group therapy sessions, not healthcare professionals' ability to deliver the intervention. Because the intervention was *delivered by* the healthcare professionals, healthcare professionals are neither research participants nor is their informed consent required.

In the CARDSS trial, all components of the intervention were *delivered to* the team of healthcare professionals. The written reports, education sessions, and involvement in the creation and implementation of action plans to improve concordance with guidelines may have impacted the interests of healthcare professionals. Therefore, healthcare professionals were research participants. As research participants, their informed consent should be sought unless the conditions for a waiver of consent obtain.

A waiver of consent for the intervention may be justifiable for healthcare professionals in the CARDSS trial. Obtaining their informed consent may have been infeasible because the intervention was delivered to the cardiac rehabilitation team as a whole; the intervention could not be divided among individual healthcare professionals. Part of the intervention included developing action plans to improve the quality of care provided by the team. Each cardiac rehabilitation team member was able to assign action plan items to any other team member. Further, the study intervention included education sessions in which recent action plans were collaboratively reviewed to improve team coordination and performance. This aspect of the intervention was delivered to the team as a whole, making it infeasible for an individual healthcare professional to refuse to consent to the intervention. For healthcare professionals, using the CARDSS Online system, receiving feedback, and creating an action plan pose minimal risk.

Unlike healthcare professionals, patients may not be research participants in some CRTs of professional-level interventions that are entirely delivered to healthcare professionals. Patients

are research participants if they are intervened upon, interacted with for data collection, or their identifiable private information is collected. Patients are commonly not research participants in CRTs evaluating professional-level knowledge translation interventions. Knowledge translation interventions that are (1) entirely delivered to healthcare professionals and (2) promote the uptake of evidence-based behaviours do not interfere with the physician's individualised judgement on behalf of her patient.[8] Healthcare professionals are free to make treatment and diagnostic decisions in accord with their fiduciary duties to patients and, as a result, these interventions do not impact the medical interests of patients. Therefore, in this type of CRT of a professional-level intervention, patients are not intervened upon. Some knowledge translation trials measure patient outcomes using only routinely collected databases with patient identifiers removed. If a patient is not intervened upon, not interacted with for data collection, and her identifiable private health information is not collected or accessed for the purposes of the study, she is not a research participant and her informed consent for research is not required. However, if one or more of these conditions obtain, patients qualify as research participants. In such cases, patient consent is required, unless conditions for a waiver of consent obtain. If patients are research participants in a CRT of a professional-level intervention, it is usually because data on their clinical outcomes are collected.

In the CARDSS trial, the intervention was not delivered to patients and did not interfere with the fiduciary duties of healthcare professionals. The intervention made healthcare professionals aware of inconsistencies between their clinical performance and established treatment guidelines. While this may have altered healthcare professionals' treatment decisions, they maintained the ability to tailor treatment to the needs of individual patients. As the physician's judgment on behalf of her patient was preserved, the patient's medical interests were not undermined by the study intervention. However, identifiable information was collected from patients in this trial. Healthcare professionals inputted deidentified patient data into the CARDSS Online System, and this deidentified data was sent to researchers. But one component of the feedback intervention required healthcare professionals in the trial to retain the ability to easily reidentify patient data so that they could discuss specific cases in detail. Therefore, patient data used in the CARDSS trial were identifiable. The use of patients' identifiable information may impact patients' interests because it places them at risk of invasions of privacy, breaches of confidentiality, and inappropriate use of their data. Therefore, patients were research participants in the CARDSS trial and their informed consent for data collection was required. Correctly, researchers obtained informed consent for data collection from patients.

CRTS OF INDIVIDUAL-LEVEL INTERVENTIONS

CRTs of individual-level interventions and individually randomised trials evaluate the same kinds of interventions. These interventions are delivered to patients and healthy volunteers. Examples of individual-level interventions include direct observed iron supplement therapy,[20] prescribed physical activity regimens,[21] and antibiotics.[22]

Consider the Prevention of Infections in Cardiac Surgery (PICS) trial.[22] It is a pragmatic CRT of an individual-level intervention that evaluated different combinations of commonly used antibiotics for the prevention of post-operative sternal surgical site infections. Patient outcomes were measured through routinely collected data and one phone call by research staff at least 90 days after surgery.

Because individual-level interventions can be tested in individually randomised trials or CRTs, researchers need to justify the use of cluster randomisation. In turn, research ethics committees need to scrutinise these justifications, because cluster randomisation should never be chosen to avoid informed consent.

The researchers in the PICS trial provided two justifications for adopting a cluster randomised design. First, they argue that the protocolized nature of the study intervention makes cluster randomisation favourable: "Cardiac surgery is conducted in specialized centers using highly standardized procedures, an approach that lends itself to a cluster [randomised] design."[22] Second, they argue that adopting a factorial cluster crossover design reduced the financial cost of the trial:

> [A] trial randomizing individual patients would likely not be feasible due to financial constraints, considering the large sample size needed to power the study properly... In contrast, if the randomization occurs at the level of the health-care center, and therefore, the study intervention becomes the standard operating procedure for that center, the resources required are significantly reduced.[22]

The first justification may be acceptable. However, given that CRTs are less statistically efficient than individually randomised trials, it is unclear how adopting a cluster randomised design reduces costs. The cluster randomised design necessarily requires a larger number of patients to account for the intracluster correlation: approximately 10% more patients in the PICS trial. The investigators are likely comparing cluster randomisation without consent to an individually randomised design with consent.

The identification of research participants is straight-forward in both individually randomised trials and CRTs of individual-level interventions because the same individual—commonly a patient—is exposed to the study intervention and the data collection procedures. In the PICS trial, patients are research participants because they were the recipient of the study intervention and they interacted with researchers for the purpose of data collection.

Considerations of informed consent are similar in individually randomised trials and CRTs of individual-level interventions because issues of consent are a function of the level of intervention, not the unit of randomisation. Both types of trials require similar justifications for a waiver of consent. Individually randomised trials rarely meet the conditions for a waiver of consent.[23] The same is true of CRTs of individual-level interventions. Generally, the administration of an individual-level intervention, in either an individually randomised trial or a CRT, involves an encounter between healthcare professional and patient. Consequently, it is typically feasible to ask for informed consent for both the study intervention and data collection at this time. The feasibility of obtaining informed consent in trials of individual-level interventions means that waivers of consent are rarely appropriate.

One difference between individually randomised trials and CRTs, including CRTs of individual-level interventions, is that clusters in CRTs may need to be randomised before participants are recruited.[24, 25] This means that when potential participants are approached for

recruitment, they cannot meaningfully decline randomisation. The function of informed consent is to allow prospective participants to adopt the ends of the study as their own before they are exposed to risk.[8] To satisfy this requirement, researchers should seek informed consent at the earliest opportunity, and before participants are exposed to the risks posed by study interventions or data collection procedures. Seeking consent from cluster members at the time of enrollment fulfills the requirements of respect for persons.[8]

As with individually randomised trials, waivers of consent in CRTs of individual-level interventions are rarely justifiable. A useful heuristic is: a waiver of consent for a CRT of an individual-level intervention should only be granted if an individually randomised trial testing the same intervention would also qualify for a waiver of consent.[26] In spite of their similarity to individually randomised trials, determining the appropriateness of waivers of consent for CRTs of individual-level interventions has been particularly challenging for research ethics committees.

Research ethics committees commonly approve waivers of consent for CRTs of individual-level interventions that do not fulfill the requirements for a waiver of consent.[27] In a systematic review of 40 CRTs of individual-level interventions, eight trials were granted a waiver of consent, but only one trial provided justifications for the waiver of consent that were consistent with regulatory criteria for a waiver of consent.[27] Illegitimately accepted justifications for waivers of consent included: the use of "usual care" study interventions; the pragmatic nature of the trial; and cluster randomisation.[27] The acceptance of these extraneous justifications creates a loophole in the ethical oversight of research.[26] Further, the illegitimate use of waivers of consent undermines the autonomy rights of participants and potentially exposes research ethics committees and their institutions to legal liability and sanction by government authorities.

To address the pressing problem of illegitimate use of waivers of consent in CRTs of individual-level intervention, a list of potential justifications for a waiver of consent and suitable follow-up questions for research ethics committees to ask researchers are found in Table 2. This table is intended to equip research ethics committees with the tools they need to navigate applications for waivers of consent in CRTs of individual-level interventions.

Table 2. Questions for putative justifications for waiver of consent in CRTs of individual-level interventions

Justification	Follow-up question for researchers
Requiring informed consent would undermine the pragmatic goals of the study.	Why would obtaining informed consent be especially detrimental to the generalisability of the trial results? Is there reason to believe that many prospective participants, if asked, would be likely to refuse?

	Have any other measures been taken to promote the generalisability of the trial (e.g., engagement with patients, patients' families, or community organisations)?
Requiring informed consent would exclude patients who require urgent care.	What proportion of surgeries/ medical care are emergency cases in the participating institutions? Can informed consent be obtained from all non-emergency cases and an emergency exemption from informed consent be sought for all emergency cases?
Requiring informed consent would exclude potential participants who are not proficient in the official languages in the region.	How many patients are expected to be excluded for this reason? Why would their exclusion be detrimental to the generalisability of this study? Is it feasible to have a translator present for the consent process?
Obtaining informed consent is impracticable because surgical/ medical care is highly protocolized.	Are there any exclusion criteria for the intervention protocol when it is used in clinical care? Are there medical contraindications (e.g., drug allergy) to any aspect of protocolized care?
Obtaining informed consent is impracticable because it would be prohibitively expensive.	Is the excessive cost attributed to the use of cluster randomisation or due to the informed consent process? What would the required sample size have been under individual randomisation? Can more statistically efficient trial designs be used? Can more cost-efficient methods of obtaining consent be used? Can more cost-efficient methods of data collection be used?
Obtaining informed consent is unnecessary because patients do not normally	In clinical practice, are treatments allocated systematically to generate knowledge that will benefit future patients? Is the treatment regimen normally allocated randomly?

decide which treatment regimen they receive.	Are there known or likely substantial or materially relevant differences between the treatment regiments in side effects, efficacy or patient burden (e.g., frequency of administration, duration of treatment)?
The interventions are minimal risk because they are usual care.	Does participating in the trial impact the trajectory of care for individual patients? Are all of these care trajectory deviations minimal risk? Are the risks of adverse effects from the interventions similar to those experienced in the everyday life of healthy individuals?

The PICS trial illustrates many of the justifications for a waiver of consent that a research ethics committee may see and need to arbitrate in CRTs of individual-level interventions. In the PICS trial, researchers justified the need for a waiver of consent by arguing that obtaining informed consent would (1) undermine generalisability and pragmatism of the trial, (2) be impracticable because cardiac surgeries are protocolized, (3) be impracticable because of cost, (4) be unnecessary because the interventions fell within the standard of care and, thus, were minimal risk, and (5) be unnecessary because in clinical practice, patients do not normally decide which treatment regimen they receive.[22] Are these acceptable justifications for a waiver of consent?

Is generalisability an acceptable justification to waive informed consent? In every clinical trial, relevant differences may distinguish those who consent to participate in the trial from those who decline participation. Seeking informed consent may thereby decrease the applicability of trial results to the target population. Although promoting generalisability is especially relevant in designing pragmatic trials, the generalisability of a trial is not more important than respecting the autonomy of participants. The requirement for the informed consent of research participants is grounded in law, human rights, and self-determination.[28] It operationalises the principle of respect for persons and is a central protection in human research. If the generalisability of a study superseded the ethical principle of respect for persons, most—if not all—research with human participants could be conducted without informed consent. Generalisability is not an acceptable justification for a waiver of consent. Rather than avoiding consent, researchers should promote generalisability in other ways, for example, by consulting stakeholders (e.g., patients, patients' families, and community organisations) during protocol design.

When an individual-level intervention is implemented as a policy, is it feasible to obtain informed consent? Cluster-level interventions are delivered to intact groups and are not divisible at the level of the individual, making it very difficult or impossible to obtain informed consent from participants. However, policies that prescribe individual-level interventions are not cluster-level interventions. Treatment policies contain medical exceptions for patients, for example excluding or offering an alternative treatment to patients with a history of allergy to the drug. This accommodation is possible because the intervention is divisible at the level of the individual. Like a medical contraindication, a patient's refusal of research participation should

exclude her. The implementation of an individual-level intervention as a policy is not a valid justification for a waiver of consent.

Is obtaining informed consent infeasible if it is expensive? Obtaining informed consent increases the cost of every clinical trial. In some cases, the costs of standard written informed consent may be prohibitively high. For example, pragmatic trials usually seek to study interventions using cost-efficient designs. Generally, cost is not a sufficient justification for a waiver of consent. If the cost of obtaining informed consent in a CRT is prohibitively expensive, then researchers should consider whether the study question can be answered with a different, less expensive design. The cost of seeking informed consent is a function of sample size and CRTs are statistically inefficient, requiring a larger sample size than an analogous individually randomised trial. Consequently, when evaluating an individual-level intervention, individual randomisation is typically more cost effective than cluster randomisation. Further, researchers should consider the use of pragmatic alternatives to standard written informed consent, such as integrated consent, verbal consent, or short form consent.[29] Healthcare professionals, as opposed to hired research staff, may be used to obtain informed consent from patients to avoid excessive costs.

Is obtaining informed consent unnecessary if patients do not normally decide which treatment regimen they receive in clinical practice? In clinical practice, there may be procedures for which informed consent is not usually obtained. For example, a patient is not typically consulted about the type of suture used to close a wound. However, the standard for informed consent in research is higher than in clinical practice.[30] Unlike clinical practice, research exposes individuals to risk at least in part for the benefit of others. Using an individual for the benefit of others heightens the need for informed consent to allow her to adopt the goals of the study as her own. Therefore, the fact that consent is not obtained for a procedure in clinical practice does not imply that consent need not be obtained in research.

Are interventions that fall within the standard of care minimal risk? At the population level, two interventions that fall within the standard of care may, on average, pose similar levels of risk to patients. However, for an individual patient, the risks of two treatments that fall within the standard of care may differ substantially.[31] For example, angiotensin converting enzyme (ACE) inhibitors and thiazide diuretics fall within the standard of care for high blood pressure, and they have similar risk profiles at the population level.[32] However, administering ACE inhibitors to pregnant patients can result in fetal harm, while administering thiazide diuretics can trigger gout attacks in patients with a history of the disease.[32]

In clinical trials, the processes of randomisation and treatment protocolization may alter the trajectory of care of individual patients. If the alteration results in a convergence of an individual risk factor with an intervention side effect, the intervention may pose more than minimal risk. If a subset of participants in the PICS trial are more susceptible to the side effects of the antibiotics (e.g., diarrhea or *Clostridium difficile* infections), and their care is altered because of the study, participating in the trial could pose more than minimal risk. For this reason, interventions that fall within the standard of care may well not be minimal risk when they are study interventions.

The PICS trial illustrates that it is difficult to justify a waiver of consent for individual-level interventions, regardless of the unit of randomisation. In the PICS trial, like all trials of individual-level interventions, the intervention is administered through an encounter with research participants. Informed consent for the study intervention and data collection can feasibly be obtained during this interaction. As with individually randomised trials, it is rarely appropriate for cluster randomised trials that involve a drug or vaccine intervention to be granted a waiver of consent.

TRANSLATING THE OTTAWA STATEMENT INTO NATIONAL REGULATORY CONTEXTS

The framework we have proposed in this paper is meant to help researchers and research ethics committees navigate issues of informed consent in CRTs. Our framework relies on the definition of a research participant and criteria for a waiver of consent that are outlined in the *Ottawa Statement*. National research regulations may differ in their definition of a research participant, and they may outline additional criteria for a waiver of consent. Therefore, additional work is required to translate our framework for application with various national research regulations.

One example of such translational work comes from the US. The Secretary's Advisory Committee on Human Research Protections (SACHRP) translated the *Ottawa Statement* recommendations to apply in the US regulatory context.[6] This body determined that many of the *Ottawa Statement* recommendations straightforwardly align with US regulations, including the need to justify cluster randomisation, the role of gatekeepers, and the need to obtain informed consent from all research participants unless the criteria for a waiver of consent obtain. However, SACHRP noted several points of divergence between the *Ottawa Statement* recommendations and US regulations. Each has a different definition of a research participant, and US regulations specify several additional criteria for a waiver of consent. Additionally, if a study aims to evaluate an intervention that alters how healthcare professionals deliver care to patients, the *Ottawa Statement* would classify it as a CRT of a professional-level intervention. In contrast, SACHRP may classify the study as a quality improvement activity—not research—if the study meets certain criteria in US guidance documents. Our purpose here is to not to weigh in on these points of disagreement, but to illustrate how ethical guidelines can be translated to apply to existing regulations. There is a need for similar translational work to be done elsewhere to apply our framework to national research regulations.

CONCLUSION

Issues of informed consent in CRTs are challenging for researchers and research ethics committees. This paper seeks to provide a three-step framework for thinking through these challenges: First, who are the research participants? Second, to what study element(s) are they exposed? And third, for each study element, is a waiver of consent appropriate? Applying this framework to CRTs of cluster-level, professional-level, and individual-level interventions demonstrates that issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation. As the popularity of CRTs continues to increase, researchers and research ethics committees must ensure that CRTs are conducted in accordance with the principle of respect for persons and the rules governing informed consent.

Figure 1. A schematic representation of how researchers and research ethics committees should navigate issues of consent in CRTs.

CONTRIBUTORSHIP STATEMENT

HPN and CW led the development of the article and wrote the first draft. All other authors (JCB, DF, CEG, and MT) provided detailed comments and revisions on subsequent drafts of the paper. All authors approved the final version of the paper.

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CW, JCB, DF, and MT are authors of the *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials.*

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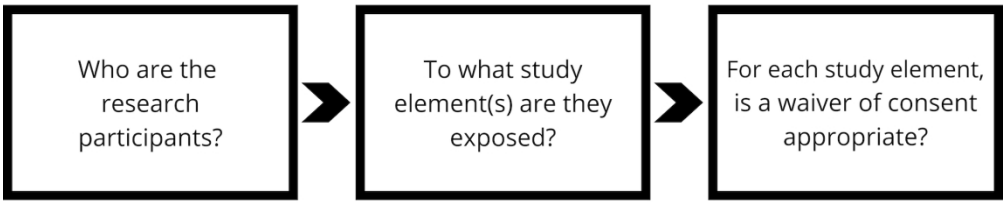

Figure 1. A schematic representation of how researchers and research ethics committees should navigate issues of informed consent in CRTs.

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