Cluster over individual randomization: are study design choices appropriately justified? Review of a random sample of trials

Running head: Justification of cluster over individual randomization

Monica Taljaard, Cory E Goldstein, Bruno Giraudeau, Stuart G Nicholls, Kelly Carroll, Spencer Phillips Hey, Jamie C Brehaut, Vipul Jairath, Alex John London, Sandra M Eldridge, Jeremy M Grimshaw, Dean A Fergusson, Charles Weijer

MT: Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), The Ottawa Hospital, Civic Campus, 1053 Carling Avenue, Ottawa, Ontario, Canada, K1Y 4E9; School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada mtaljaard@ohri.ca
Senior Scientist (613) 798-8899 ext. 18618

CEG: Rotman Institute of Philosophy, Western University, WIRB 7175, 1151 Richmond Street London, ON, Canada, N6A 5B7. cgoldst2@uwo.ca
PhD Candidate (Philosophy)

BG: Université de Tours, Université de Nantes, INSERM, SPHERE U1246, Tours, France; INSERM CIC1415, CHRU de Tours, Tours, France. bruno.giraudeau@univ-tours.fr
Professor

SGN: Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), The Ottawa Hospital, Civic Campus, 1053 Carling Avenue, Ottawa, Ontario, Canada, K1Y 4E9; snicholls@ohri.ca
Senior Clinical Research Associate

KC: Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), The Ottawa Hospital, General Campus, 501 Smyth Road, Ottawa, Canada, K1H 8L6; kecarroll@ohri.ca
Research Coordinator

SPH: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont Street, Boston, MA, USA, 02120; Center for Bioethics, Harvard Medical School, Boston, MA, USA. shey@bwh.harvard.edu
Research Scientist

JCB: Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), The Ottawa Hospital; General Campus, 501 Smyth Road, Ottawa, Canada, K1H 8L6; School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada. jbrehaut@ohri.ca
Senior Scientist

JMG: Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), The Ottawa Hospital, General Campus, 501 Smyth Road, Ottawa, Ontario, Canada, K1H 8L6; Department of

Medicine University of Ottawa, Ottawa, Canada; School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada. jgrimshaw@ohri.ca
Senior Scientist

VJ: Division of Gastroenterology, Department of Medicine, Western University, London, Ontario, Canada. Division of Epidemiology and Biostatistics, Western University, University Hospital, 339 Windermere Road, London, Ontario, Canada, N6A 5A5. vjairath@uwo.ca
Scientist

SME: Centre for Primary Care and Public Health, Queen Mary University of London, 58 Turner Street, London, UK, E1 2AB. s.eldridge@qmul.ac.uk
Professor

AJL: Department of Philosophy and Center for Ethics and Policy, Carnegie Mellon University, 150A Baker Hall, Pittsburgh, PA, USA, 15213-3890. ajlondon@andrew.cmu.edu
Professor

DAF: Clinical Epidemiology Program, Ottawa Hospital Research Institute (OHRI), The Ottawa Hospital, General Campus, 501 Smyth Road, Ottawa, Ontario, Canada, K1H 8L6; Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada. dafergusson@ohri.ca
Senior Scientist

CW: Rotman Institute of Philosophy, Western University, WIRB 7160, 1151 Richmond Street, London, ON, Canada, N6A 5B7 cweijer@uwo.ca
Professor

Corresponding author: Monica Taljaard

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ABSTRACT (417 words/ MAX 425)

Objectives: Novel rationales for randomizing clusters rather than individuals appear to be emerging from the push for more pragmatic trials, for example to facilitate trial recruitment, reduce the costs of the research, and improve external validity. Such rationales may be driven by a mistaken perception that choosing cluster randomization lessens the need for informed consent. We reviewed a random sample of published cluster randomized trials (CRTs) involving only individual-level health care interventions to determine: (a) the prevalence of reporting a rationale for the choice of cluster randomization; (b) the types of explicit, or if absent, *apparent* rationales for the use of cluster randomization; (c) the prevalence of reporting patient informed consent for study interventions; and (d) the types of justifications provided for waivers of consent. We considered CRTs evaluating exclusively individual-level health care interventions to focus on clinical trials where individual randomization is theoretically possible and where there is a general expectation of informed consent.

Design: A random sample of 40 CRTs identified through implementing a validated electronic search filter in two electronic databases (Ovid Medline and Embase) with two reviewers independently extracting information from each trial.

Setting: Inclusion criteria were: primary report of a CRT; evaluating exclusively an individual-level health care intervention(s); published between 2007-2016; and conducted in Canada, USA, European Union, Australia, or low-and-middle-income country (LMIC) settings.

Results: Twenty-five trials (62.5%, 95% confidence interval (CI) 47.5 to 77.5%) reported an explicit rationale for the use of cluster randomization. The most commonly reported rationales were logistical or administrative convenience (15 trials, 60%) and the need to avoid contamination (13, 52%); 5 trials (20%) cited rationales related to the push for more pragmatic

trials. Twenty-one trials (52.5%, 95% CI 37 to 68%) reported written informed consent for the intervention, 2 (5%) reported verbal consent, 8 (20%) reported waivers of consent, while in 9 (22.5%) consent was unclear or not mentioned. Reported justifications for waivers of consent included that study interventions were already used in clinical practice, patients were not randomized individually, and to facilitate the pragmatic nature of the trial. Only one trial reported an explicit and appropriate justification for waiver of consent based on minimum criteria in international research ethics guidelines, namely infeasibility and minimal risk.

Conclusions: Rationales for adopting cluster over individual randomization and for adopting consent waivers are emerging, related to the need to facilitate pragmatic trial aims. Greater attention to clear reporting of study design rationales, informed consent procedures, as well as justification for waivers is needed to ensure that such trials meet appropriate ethical standards.

KEY WORDS

Cluster randomized trials; pragmatic trials; informed consent; research ethics review; waivers of consent

INTRODUCTION

In an individually randomized controlled clinical trial, patients are independently recruited (after soliciting their informed consent), randomized to receive one or more experimental or control interventions, and observed for their outcomes. In a cluster randomized trial (CRT) however, the units of randomization are groups such as hospitals or medical practices, while the units of observation are the patients.[1] A key implication of cluster randomization is that, because outcomes from multiple patients in the same cluster are usually positively correlated, a larger sample size is required than if individual randomization were used.[1] The sample size inflation factor is a function of the cluster size and the intracluster correlation coefficient, and can be substantial. For example, with a commonly assumed intracluster correlation coefficient of 0.05 and a cluster size of 100, the number of patients required for a parallel arm CRT is six times that under individual randomization. Another key implication is that CRTs are subject to increased risks of bias. Often, individual patients must be identified and recruited after cluster randomization and unless this is done blinded to the cluster's allocation (which can be difficult or impossible to ensure), differential inclusion of patients may result.[2,3] CRTs typically randomize fewer units than individually randomized trials, and although the risks of chance bias due to baseline imbalances do not necessarily decrease with sample size,[4] interpretation of trial results may be more complicated when substantial baseline differences exist. As it is unethical to expose people to research risks without adequate social value, a clear justification for the use of cluster randomization is required.[5,6] The recently revised Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Health-related Research Involving Humans,* for example, holds that adequate social value is a necessary condition for ethically acceptable research with humans and that "[i]t is essential to the

social value of health-related research that its design is scientifically sound and that it offers a means of developing information not otherwise obtainable."[7] Providing an acceptable rationale for choosing cluster, as opposed to individual, randomization should therefore establish why the increased risks of bias and the use of larger sample sizes are justified relative to the alternative of an individually randomized trial. In this manuscript, we consider ethical issues raised by the choice of cluster over individual randomization.

CRTs may involve several different types of intervention. The nature of the intervention can influence the rationale for a CRT. Where cluster randomised trials involve interventions referred to as "cluster-cluster" and "professional-cluster" interventions,[8] the choice of cluster randomization is obvious as individual randomization is simply not feasible. A cluster-cluster intervention is such that it can only be delivered to the entire cluster, i.e., it is not divisible at the individual-level (for example, an engineering system to reduce the saltwater content of central water supplies in rural coastal areas).[9] A professional-cluster intervention is delivered to health providers (for example, education to improve their prescribing practices).[10] However, in this paper, we examine CRTs that only include "individual-cluster" interventions, in particular, clinical interventions such as supplementation of pregnant women with vitamin A or beta carotene.[11] In these trials, patients could theoretically opt out of receiving interventions and individual randomization is therefore possible. While no explicit guidance exists to determine what are acceptable rationales for adopting cluster randomization, commonly used rationales and their application to individual-level health care interventions, are summarized in Supplementary Table 1. The burden is on investigators to justify their choice of study design, although the legitimacy of such justifications can often be difficult to determine.

In recent years, there has been a renewed interest in the use of cluster randomization for pragmatic comparative effectiveness research, designed to compare the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care in real-world (as opposed to optimized) conditions.[12,13] Key considerations in discussions about study designs for pragmatic comparative effectiveness research are generalizability, logistics and costs of the research, with cluster randomization being perceived as offering advantages over individual randomization. For example, individual randomization has been described as onerous and costly, while cluster randomization is the preferred method to evaluate questions of effectiveness due to "their enhanced external validity and lower costs".[14] We have identified such statements as a concern,[15] indicating that investigators might be conflating the use of cluster randomization with waivers of informed consent. Because CRTs require *more* patients (and usually more centers) than individually randomized trials, CRTs may cost *more* than individually randomized trials, holding consent procedures fixed. Likewise, CRTs do not necessarily translate to greater external validity; individually randomized trials can be designed to be highly pragmatic and generalizable. The perception that cluster randomization by itself increases the degree of pragmatism and external validity may rest on the misperception that the design facilitates inclusion of whole clusters without the need for informed consent. Others have explicitly argued that "consent for the intervention is not relevant in a cluster randomized trial because patients receive the same treatment regardless of whether or not they consent."[16] Moreover, two recently published articles on pragmatic trials referred to CRTs as being able to help avoid or lessen the need for informed consent.[17,18] However, informed consent is a fundamental requirement in international research ethics guidance: a research ethics committee may approve a modification or waiver of informed consent only if the research would not be

feasible without the waiver or modification, the research has important social value, and the research poses no more than minimal risk to participants.[7] If researchers and research ethics committees are mistakenly accepting design rationales that amount to the ability to circumvent established research ethics requirements, then it creates the potential for the inadvertent or explicit gaming of the research ethics system.[19]

In this study, our primary objectives were to examine rationales for using cluster randomization, as well as reporting of informed consent and justifications for waivers of consent in a random sample of trials exclusively evaluating individual-cluster interventions. Our focus is on CRTs where clusters consist of multiple individuals, as opposed to CRTs where each individual constitutes a cluster and provides multiple observations, say, on different body parts. Our hypothesis was that there are emerging justifications for adopting cluster randomization stemming from the rising interest in pragmatic trials, but that these may be accompanied by the mistaken perception that choosing cluster randomization lessens the need for informed consent. As it is improbable that investigators would explicitly state that they chose cluster randomization to avoid seeking informed consent, we set out to determine: (a) the prevalence of reporting a rationale for the choice of cluster randomization; (b) the types of explicit, or if absent, *apparent* rationales for the use of cluster randomization; (c) the prevalence of reporting informed consent for study interventions; and (d) the types of justifications provided for waivers of consent.

METHODS

Identification of relevant articles

We adapted our previously published and validated electronic search filter to identify CRTs published during or after 2007 to cover a 10-year period at the time of the search.[20] We considered trials published in the past 10 years because this corresponds to a period with increasing attention on pragmatic comparative effectiveness research. The search filter, presented in Supplementary Table 2, was implemented on 16 November 2016 in two databases: Ovid Medline and Embase. The records were manually de-duplicated and imported into Covidence software.[21] Title and abstract screening was a two-stage process: two reviewers (MT, ARH) independently screened records to identify "possible CRTs", followed by two reviewers (MT, KC) independently screening this subset of records to identify primary reports of CRTs. Records were excluded if they were a protocol or design paper, secondary outcome analysis, process evaluation, or baseline evaluation.

All citations of possible primary reports of CRTs were then exported to an Excel spreadsheet. To operationalize random selection, we generated a uniform random number for each record using Excel's RAND function and then ordered the records by that number. A single reviewer (KC) then screened the full text articles for each record in sequence until our target sample size was achieved. Inclusion criteria were: a) primary report of a CRT; b) evaluating an exclusively individual-level health care intervention; and c) conducted in Canada, USA, European Union, Australia, or LMIC settings (the countries in which our investigator team has experience). Individual-level interventions were defined as any intervention that is divisible (implemented) at the individual-level; thus, CRTs were excluded if they evaluated a complex intervention that involved cluster-level or professional-level interventions. Health care interventions were defined as any pharmacological interventions, pharmacological treatment strategies (e.g., different timing of taking medications), surgical interventions, implantable or

non-implantable devices, rehabilitation, diet, or other types of clinical interventions. Trials of public health, and health promotion and prevention interventions were excluded. Thus, we considered clinical trials in which individual randomization might be possible and where there is a general expectation of patient informed consent.

Sample size

Our target sample size was 40 trials, based on being able to conduct the review within the constraints of an unfunded study.

Data abstraction

Data abstraction forms used in our previous reviews[22,23] were adapted for the specific purposes of this review, and pilot tested using an initial convenience sample of eight eligible CRTs identified through PubMed searches. All five reviewers (MT, SGN, KC, ARH, and CEG) participated in the pilot testing and any discrepancies in abstraction were resolved by discussion among all reviewers. The remaining 32 trials were then distributed amongst the reviewers and abstracted independently by two reviewers per trial. Each reviewer pair included both ethics and methods expertise. After each batch of three trials had been abstracted, discrepancies were reviewed within the pair and resolved by consensus. If differences could not be resolved, either CW or MT were final arbitrators. The primary source of information for each trial was the published report, but we accessed any supplementary information that was available online, including study protocols, supplementary information or informed consent sheets.

Data were abstracted on trial characteristics, including publication year, country of study recruitment, type of cluster, and study design. We also extracted whether the study was self-identified as a pragmatic trial, and the reported use of a data safety monitoring committee and

research ethics review. We recorded detailed information about study interventions and data collection procedures in each arm of the trial. If there was more than one trial arm, abstractors were asked to reach consensus, before extractions, in classifying one arm as the main intervention arm and one arm as the comparator. We recorded whether interventions were explicitly reported as usual care or "standard of care". Trial data collection was classified as review of patient medical records, data query from a clinical data registry or other central source of routinely collected data, or the use of any direct intervention upon or interaction with participants for data collection, including physical examination not required for normal patient care, or interactions such as specimen collection, surveys or interviews.

For each trial, we recorded whether there was an explicit rationale provided for the choice of a CRT design, as required by the CONSORT extension for CRTs.[6] We also classified the type of rationale as one or more of the following: to avoid treatment contamination, logistical or administrative convenience, to reduce trial costs, to enhance compliance, to secure cooperation of clusters, to achieve herd immunity or study direct and indirect effects of interventions in infectious disease settings, and other (with explanation). Within the category of "other", we identified any rationales that referred to the need to facilitate pragmatic trial design. When no rationale was provided, abstractors were asked to indicate any apparent rationale, using their judgement.

Informed consent in CRTs can apply with respect to study interventions or data collection (or both), thus we abstracted such information separately.[24] We classified the type of consent (if reported) as written, verbal, deferred, or waived or no consent; we also classified cases where consent was unclear or not mentioned. In case of a waiver of consent, we recorded any reported justification for the waiver.

Analysis

We conducted a descriptive synthesis of the characteristics and features of included studies, summarizing results using frequencies and percentages for categorical variables and medians and interquartile intervals for continuous variables. Two-sided 95% confidence intervals were calculated for the main outcomes.

RESULTS

Identification of relevant articles

The flow diagram depicting the identification and screening of articles is presented in Figure 1. Database searching identified 10,045 records; 3,097 possible primary reports of CRTs remained after pre-processing and were exported to an Excel spreadsheet and sorted in random sequence for full-text searching (Figure 1). A total of 1,198 articles had to be screened to identify the required sample. The main reasons for excluding articles at the full-text stage were non-health care interventions, or interventions included some cluster-level or professional-level components.

Description of included studies

Characteristics of the included trials are presented in Table 1. Trials were conducted in 27 different countries; about half were in a LMIC. Units of randomization were diverse, but the most commonly used were residential areas, hospitals and intensive care units (ICUs). The median of the number of clusters randomized was 24 and median of the average cluster size analysed for the primary outcome was 115. The majority used a parallel arm design, but cluster

cross-overs and stepped wedge trials[25] were also present in our sample. All but one study reported review by a research ethics committee. Less than half self-identified as pragmatic. The majority of trials used an active control (i.e., comparative effectiveness research), while less than a quarter reported a non-protocolized control arm. The 40 trials included in our sample were published in 21 different journals (Supplementary Table 3) with impact factors ranging from 1.12 to 59.56 (median 14.43).

Study interventions and data collection procedures

Characteristics of the study interventions and data collection procedures are presented in Table 2. The most commonly used intervention type was pharmacological or pharmacological treatment strategy. The intervention was explicitly reported by investigators as "usual care" or "standard of care" in 7 trials. Close to half of the trials used data extracted from patient medical records. Over half used specimen collection (such as blood tests) or physical examination not required for normal patient care, and over half involved interaction with patients through completion of study questionnaires. Nine trials used solely routinely collected data (e.g., review of patient medical charts or downloaded data from a central source).

Rationale for the use of cluster randomization

Reported and apparent rationales for adopting cluster randomization are presented in Table 3. A total of 25 trials (62.5%, 95% confidence interval (CI) 47.5 to 77.5%) provided an explicit rationale for the use of cluster randomization, while 15 (37.5%) provided no rationale. The median (25^{th} to 75^{th} percentile) journal impact factor for trials with an explicit rationale was 14.4 (3.6 to 39.2) and without an explicit rationale 11 (4.2 to 39.1). More than one rationale was possible in any trial. The most commonly reported rationales were logistical or administrative

convenience and the need to avoid contamination (over half of trials). Five trials reported rationales related to the need for a more pragmatic trial or to ensure external validity. Other reported reasons were to enhance compliance, to reduce study costs, to achieve herd immunity or study direct and indirect effects of interventions in infectious disease settings, to secure cooperation of clusters, and to maintain blinding. Among the 15 trials with no explicit rationale for cluster randomization provided, reviewers could identify a possible or apparent rationale in all 15.

Informed consent

Reporting of informed consent in the intervention and control arms was similar and we present information only for the intervention arm in Table 4. A total of 21 trials (52.5%, 95% CI 37 to 68%) reported seeking written informed consent for the study intervention, while 2 (5%) reported verbal informed consent; 8 (20%) reported a waiver of consent, while in 9 (22.5%), consent for the intervention was either not mentioned or it was unclear. With respect to consent for data collection, 20 trials (50%) reported written informed consent for data collection, while 3 (7.5%) reported verbal consent; 3 (7.5%) reported a waiver of consent, while in 14 (35%), consent for data collection was not mentioned or it was unclear. The median (25^{th} to 75^{th} percentile) journal impact factor for the 23 trials reporting written or verbal informed consent for study interventions was 5.22 (3.53 to 38.28) and for the remaining 17 trials was 30.8 (5.78 to 47.05).

Justifications for consent waivers were reported in 6 of 8 trials with waivers of consent for study interventions. Only one trial provided a justification consistent with international research ethics guidelines, by stating that the study constitutes no more than minimal risk, the

research could not be carried out without a waiver, the waiver will not adversely affect the rights and welfare of patients, and patients will be provided with pertinent information. Other provided reasons were: interventions are usual care interventions involving only minimal risk; the interventions constitute standard of care and patients were given pertinent information by means of posters placed in waiting rooms; the waiver was justified because of the pragmatic nature of the trial; the research was conducted in an emergency situation; consent was unnecessary because patients were not randomized individually and interventions are commonly used in current practice.

Association between reporting a rationale for cluster randomization and informed consent

Table 5 presents the association between reporting of written or verbal consent for study interventions and rationales for cluster randomization. When considering the trials with explicit rationale provided for cluster randomization, just over half reported either written or verbal consent for the study intervention; this proportion was slightly higher among trials without explicit rationales. The reporting of written or verbal consent varied according to the type of rationale, ranging from a prevalence of 40% among trials with pragmatic rationales, to 75% among trials with rationales related to herd immunity.

DISCUSSION

Our review of a random sample of 40 reports of individual-cluster trials with health care interventions found that just over half reported written informed consent for study interventions, while one in five explicitly reported a waiver of consent. Justifications for waivers were not

always provided and when provided, were consistent with minimum criteria for waivers outlined in international research ethics guidance in only one trial. Further, contrary to reporting requirements for CRTs,[6] more than a third of trials did not report a clear rationale for the use of the CRT design. When a rationale for the use of a CRT design was provided, the most common rationales were logistical or administrative convenience and the need to avoid contamination. We also found justifications for the use of cluster randomization and waivers of consent related to the need to facilitate the pragmatic aims of the trial.

We did not anticipate the need to avoid contamination to be a frequently used rationale as our study was focused on clinical interventions such as pharmacological treatments; we excluded trials of behavioural, educational or health promotion interventions in which the risk of contamination might be higher (for example, due to individuals in the same cluster sharing information about the trial). A possible explanation is that many of our trials were conducted in LMIC settings in which randomization errors within communities and medication sharing can contribute to a form of contamination. Furthermore, nearly half of the trials in our sample involved pharmacological treatment strategies (rather than pharmacological treatments per se) in which there may be a risk of contamination when the same provider is expected to administer the intervention to multiple patients in their care.

Our study has several limitations. First, our sample size of 40 trials was based on logistical considerations and is small (although it is similar to sample sizes in two other reviews that considered design justifications for CRTs).[26,23] Second, our results are dependent on the completeness and clarity of reporting, and we did not contact corresponding authors to obtain additional information. However, given that we were interested in documenting the quality of reporting, and the presence of trial design and reporting practices that are ethically problematic,

asking investigators to explain their design choices after the fact runs the risk of them providing a post-hoc justification that would not be a true indicator of the pre-trial rationale. Third, we could not classify rationales as appropriate or inappropriate, as it was not possible to dispute a provided rationale without detailed knowledge of the trial; thus, we were unable to examine the extent to which investigators might be adopting cluster randomization under the mistaken perception that it can avoid or lessen the need for informed consent.

To our knowledge, this is the first study to examine rationales for the choice of cluster randomization in the case of exclusively individual-level interventions and the relationship to consent practices in the trial. In a review of a random sample of 300 CRTs from 2000-2008, 94 (31%) reported a rationale for the use of cluster randomization, and 178 (59%) reported individual-level consent for any aspect of the trial (data collection, study interventions),[22] but that review did not consider the subset of trials with exclusively individual-level health care interventions. Brierley and colleagues reviewed 24 CRTs published in 2008 in four leading medical journals to identify studies in which individual randomization may have been possible and to assess the risk of selection bias.[26] They found that in 16 (67%), there was a clear rationale for cluster randomization and individual randomization would not have been possible. The main reasons identified for cluster randomization were to avoid contamination, logistical considerations especially in LMIC settings, and the use of cluster-level interventions.

The adequacy of justifications for adopting cluster randomization with waivers of consent has received little attention, yet, such designs are becoming increasingly possible with the availability of routinely collected data for outcome assessment. By eliminating the need to recruit, randomize and follow individual patients within each center, such designs can substantially reduce the costs and logistical complexity of the research, promote external validity

by facilitating the inclusion of entire patient populations and centers that may lack research infrastructure, and promote internal validity by avoiding a key risk of bias due to post-randomization recruitment. However, there is a concern that potential misconceptions over the use of waivers of consent and logistical advantages to this design that derive from avoiding research ethics requirements, might create the potential for the gaming of research oversight processes. Generally, CRTs involving human research participants should be considered research and submitted for approval by a research ethics committee. Funders, research ethics committees and journal editors should require investigators to provide a clear rationale for the choice of cluster over individual randomization. Individual randomization should generally be preferred as it avoids risks of identification and recruitment biases, as well as the sample size penalty of cluster randomization.[27] Furthermore, researchers, regulators and research ethics committees need to apply the same standard for a waiver of informed consent, regardless of trial design, i.e., infeasibility without the waiver, research is of important social value, and poses minimal risks of harm.[7] The use of cluster randomization, in itself, should not imply a lower standard for informed consent.[5] It is possible that investigators perceive research ethics committees as being more inclined to grant waivers of consent for an intervention when it is evaluated in a cluster randomized design than in an individually randomized design, because the larger sample size required by a cluster randomized design makes it easier to justify the waiver based on the infeasibility criterion — but this is circular reasoning. The decision to adopt cluster rather than individual randomization should be independently justified using scientific, practical, and logistical considerations — whether a waiver of consent for an individual-level intervention is appropriate is a separate issue.

While individual-cluster trials are currently a small fraction of all CRTs, we anticipate that there will be a rise in the use of this design with the increasing emphasis on pragmatic comparative effectiveness research.[28] Explicit guidance regarding alternative approaches to consent (other than waivers) that are compatible with pragmatic trial aims is needed, for example, integrated consent.[29] Guidance is also needed on what constitutes "infeasibility" of consent, as opposed to mere inconvenience or inefficiency: a recent review of international ethics guidance indicated no consensus on when informed can be waived for infeasibility reasons.[30] Finally, explicit guidance is needed to help researchers and research ethics committees judge the legitimacy of CRT design justifications, including when individual-level interventions can be conceptualized as cluster-level policies (thus, implying the need for cluster randomization). Our international, interdisciplinary team has recently been funded to study these issues in more depth and to develop guidance for the ethical design and conduct of pragmatic randomized controlled trials.[31]

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CONTRIBUTORS

The study was conceived by MT and CW. MT, CW, DAF, CEG, and BG contributed to the development of the data extraction form. MT and KC screened studies. MT, KC, CEG, and SGN extracted data. MT conducted the statistical analysis. MT wrote the first draft of the manuscript. All authors were responsible for the critical review of the manuscript. All authors had full access to the data in the study and MT takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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DECLARATION OF CONFLICTING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare. CW receives consulting income from Eli Lilly & Company Canada. Other authors report no support from any organisation for the submitted work;

no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

ETHICAL APPROVAL

Not required.

Table 1: Characteristics of trials included in review (N=40)

Characteristic	Frequency (%)
Publication year	
2007-2010	9 (22.5%)
2011-2013	20 (50.0%)
2014-2016	11 (27.5%)
Journal Impact Factor	
Median (Q1-Q3)	14.4 (3.6 – 39.2)
Country of study conduct	
Canada	1 (2.5%)
USA	5 (12.5%)
Canada and USA	1 (2.5%)
United Kingdom	4 (10%)
Elsewhere in the European Union	7 (17.5%)
Australia	1 (2.5%)
LMICs	21 (52.5%)
Types of clusters	
Residential areas	15 (37.5%)
Primary care practices	4 (10%)
Individual health professionals	2 (5%)
Hospitals	6 (15%)
Nursing homes	3 (7.5%)
Medical clinics	2 (5%)
Intensive Care Units	4 (10%)
Other	4 (10%)
Funding source	
Industry alone	1 (2.5%)
Government alone	13 (32.5%)
Foundation/university alone	10 (25.0%)
Multiple sources of funding	15 (37.5%)
None reported	1 (2.5%)
Number of clusters randomized	
Median (Q1-Q3)	24 (12.5 – 52.5)
Average cluster size	
Median (Q1-Q3)	115 (35 – 391)
Trial design	
Parallel arm	28 (70%)
Factorial	3 (7.5%)
Cross-over	6 (15%)
Stepped wedge	3 (7.5%)
Reported presence of a DSMC	16 (40%)
Self-identified as pragmatic trial	16 (40%)
Research ethics review reported	39 (97.5%)
Type of control arm	
Non-protocolized care (no active intervention)	9 (22.5%)

Placebo or sham treatment	2 (5%)
Augmented care	2 (5%)
Active control (alternative health care intervention)	24 (60%)
Other (e.g., vaccine for an unrelated condition)	3 (7.5%)

DSMC = Data Safety Monitoring Committee
LMIC = Low-and-Middle-Income Country
Q1=First quartile
Q3=Third quartile

Table 2: Characteristics of study interventions and data collection procedures included in review (N=40)

Characteristics	Intervention arm Frequency (%)	Control arm Frequency (%)
Types of study interventions*		
Pharmacological	23 (57.5%)	13 (41.9%)
Pharmacological treatment strategy	19 (47.5%)	13 (41.9%)
Non-pharmacological treatment strategy	7 (17.5%)	9 (29.0%)
Non-implantable device	1 (2.5%)	1 (2.5%)
Study interventions reported as "usual care" or "standard of care"?		
Yes	7 (17.5%)	34 (85%)
No	32 (80%)	3 (7.5%)
Unclear	1 (2.5%)	3 (7.5%)
Types of data collection interventions		
Review of medical records	19 (47.5%)	19 (47.5%)
Clinical registry or routine database	8 (20%)	8 (20%)
Specimen collection or physical exam not required for normal patient care	23 (57.5%)	22 (55%)
Interviewer-administered questionnaire	17 (42.5%)	17 (42.5%)
Self-administered questionnaire	7 (17.5%)	6 (15%)
Primary data collection (electronic case record forms)	13 (32.5%)	13 (32.5%)
Solely routinely collected data	9 (22.5%)	9 (22.5%)

*A trial could be classified as having more than one type of intervention.

Table 3: Reported and apparent rationales for the use of cluster randomization (N=40)

	Frequency (%)
Trials with explicit rationale provided	25 (62.5%)
Type of rationale provided*	
Logistical or administrative convenience	15 (60%)
To avoid contamination	13 (52%)
To be more pragmatic or enhance external validity	5 (20%)
To enhance compliance	5 (20%)
To reduce costs	3 (12%)
Herd immunity or to study direct and indirect effects of interventions	4 (16%)
To secure cooperation of clusters	2 (8%)
To maintain blinding	2 (8%)
Trials with no explicit rationale provided	15 (37.5%)
Apparent rationale (in reviewers' judgement)*	
Logistical or administrative convenience	13 (86.7%)
To avoid contamination	7 (46.7%)
Herd immunity or to study direct and indirect effects of interventions	8 (53.3%)
To allow physicians to prescribe the same treatment for all their patients	2 (13.3%)

*A trial could be classified as having more than one type of rationale.

Table 4: Reporting of informed consent procedures in the intervention arm (N=40)

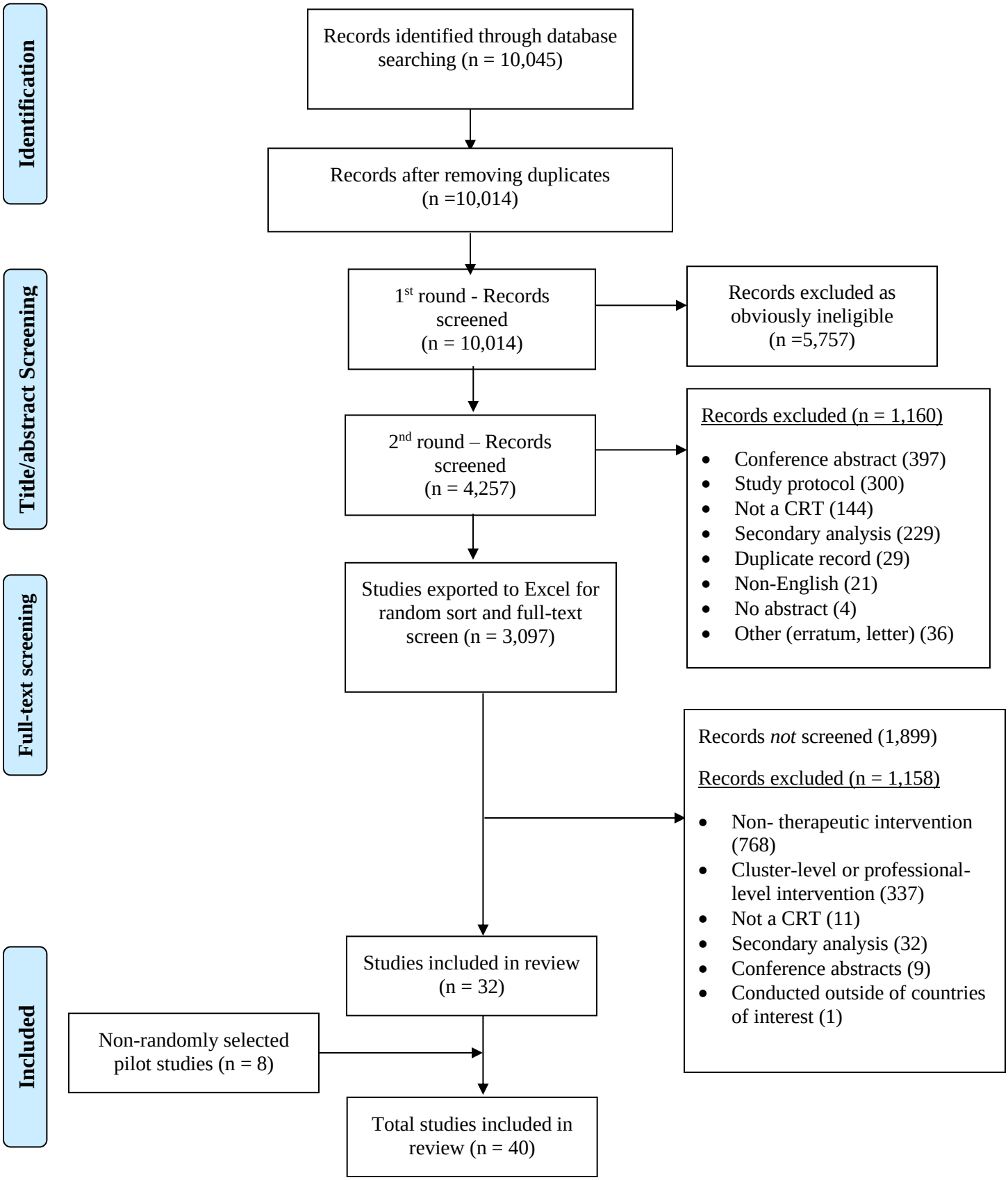
Characteristics	Frequency (%)
Consent for study interventions	
Written informed consent	21 (52.5%)
Verbal informed consent	2 (5%)
Waiver of consent or no consent	8 (20%)
Consent unclear or not mentioned	9 (22.5%
Consent for data collection	
Written informed consent	20 (50%)
Verbal informed consent	3 (7.5%)
Waiver of consent or no consent	3 (7.5%)
Consent unclear or not mentioned	14 (35%)
Any consent	
Explicitly reported written or verbal consent for both study interventions and data collection	18 (45%)
Explicitly reported waiver of consent for both study interventions and data collection	3 (7.5%)
Explicitly reported waiver of consent for study intervention but written or verbal consent for data collection	3 (7.5%)
Unclear	16 (40%)

Table 5: Association between rationales for the use of cluster randomization and reporting of written or verbal informed consent (N=40)

	Frequency (%)	Written or verbal consent for study interventions?	
		Yes	No
Trials with explicit rationale provided	25 (62.5%)	13 (52.0%)	12 (48%)
Type of rationale provided			
Logistical or administrative convenience	15 (60%)	8 (53.3%)	7 (46.7%)
To avoid contamination	13 (52%)	7 (53.9%)	6 (46.2%)
To be more pragmatic or enhance external validity	5 (20%)	2 (40%)	3 (60%)
To enhance compliance	5 (20%)	3 (60%)	2 (40%)
To reduce costs	3 (12%)	1 (33.3%)	2 (66.7%)
Herd immunity or to study direct and indirect effects of interventions	4 (16%)	3 (75%)	1 (25%)
To secure cooperation of clusters	2 (8%)	1 (50%)	1 (50%)
To maintain blinding	2 (8%)	1 (50%)	1 (50%)
Trials with no explicit rationale provided	15 (37.5%)	10 (66.7%)	5 (33.3%)
Apparent rationale (in reviewers' judgement)			
Logistical or administrative convenience	13 (86.7%)	9 (69.2%)	4 (30.8%)
To avoid contamination	7 (46.7%)	5 (71.4%)	2 (28.6%)
Herd immunity or to study direct and indirect effects of interventions	8 (53.3%)	5 (62.5%)	3 (37.5%)
To allow physicians to prescribe the same treatment for all their patients	2 (13.3%)	2 (100%)	0

FIGURE LEGENDS

Figure 1: Study flow diagram


Identification
Title/abstract Screening
Full-text screening
Included
Records identified through database searching (n = 10,045)
Records after removing duplicates (n =10,014)
1st round - Records screened (n = 10,014)
Records excluded as obviously ineligible (n =5,757)
2nd round – Records screened (n = 4,257)
Records excluded (n = 1,160)
Conference abstract (397)
Study protocol (300)
Not a CRT (144)
Secondary analysis (229)
Duplicate record (29)
Non-English (21)
No abstract (4)
Other (erratum, letter) (36)
Studies exported to Excel for random sort and full-text screen (n = 3,097)
Records not screened (1,899)
Records excluded (n = 1,158)
Non- therapeutic intervention (768)
Cluster-level or professional-level intervention (337)
Not a CRT (11)
Secondary analysis (32)
Conference abstracts (9)
Conducted outside of countries of interest (1)
Studies included in review (n = 32)
Non-randomly selected pilot studies (n = 8)
Total studies included in review (n = 40)

Supplementary Table 1: Common reasons for adopting cluster randomization and applicability to individual-cluster trials with therapeutic interventions

Reason	Explanation	Usually applies to individual health-care interventions?
Intervention is inherently a cluster-level intervention	Due to the nature of the intervention, exposure is involuntary, and cluster randomization is the only feasible choice	No
Intervention is administered to health professionals in each cluster	In case of educational or behaviour change interventions, it would not be appropriate or feasible to ask professionals to treat both experimental and control patients	No
To avoid a high risk of treatment contamination	In case of behavioural, educational, or health promotion interventions, individuals in the same cluster but randomized to different arms may share information about the trial and bias the intervention effect towards the null; in LMIC settings, community members may share medications to increase the chances of receiving an active treatment	May apply, especially in LMIC settings
To simplify trial logistics	It can simplify the trial organization if there is only one type of treatment in each cluster; in LMIC settings, it can minimize the risk of errors if fieldworkers only need one type of treatment in their possession and don't have to keep track of individual allocations	Yes, especially in LMIC settings
To reduce costs	When the intervention involves provision of staff or expensive equipment, a CRT can reduce costs in that only half of participating sites need to be supplied rather than all sites	Not usually; a CRT increases the sample size and therefore, costs of recruitment
Herd immunity or to study direct and indirect effect of intervention	In trials of treatments for infectious diseases, individual randomization might be impractical because some individuals allocated to the control arm may nevertheless receive protection through herd immunity; moreover, both direct and indirect effects of intervention may be of interest	Applies to some types of treatments
To enhance compliance	For some interventions (e.g., behavioural or health promotion), compliance may be enhanced through interactions amongst cluster members	Not generally
To facilitate recruitment	Gatekeepers or communities may not be willing to participate unless all their members receive intervention; to avoid resentment amongst community members who don't receive an intervention perceived to be beneficial	May apply to some types of treatments, especially in LMIC settings

LMIC = Low-and-Middle-Income Country

Supplementary Table 2: Electronic search filter to identify cluster randomized trials

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>
Search Strategy:

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1. controlled trial.pt. (469686)
2. Analysis/ (58846)
3. (cluster* adj2 random*).tw. (11394)
4. ((communit* adj2 intervention*) or (communit* adj2 randomi*)).tw. (6985)
5. group* randomi*.tw. (2887)
6. or/2-5 (77174)
7. 1 and 6 (8878)
8. cluster rct*.tw. (422)
9. (cluster adj2 random* controlled trial*).tw. (3745)
10. 7 or 8 or 9 (10275)
11. limit 10 to yr="2007 -Current" (8642)
12. animals/ not humans/ (4635939)
13. 11 not 12 (8624)

Database: Embase Classic+Embase <1947 to 2016 November 16>
Search Strategy:

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1. double-blind*.mp. or placebo*.tw. or blind*.tw. (497090)
2. *randomized controlled trial/ (37865)
3. 1 or 2 (523172)
4. cluster analysis/ (48160)
5. (cluster* adj2 random*).tw. (11592)
6. ((communit* adj2 intervention*) or (communit* adj2 randomi*)).tw. (7433)
7. group* randomi*.tw. (2881)
8. or/4-7 (67327)
9. 3 and 8 (4327)
10. cluster rct*.tw. (392)
11. (cluster adj5 trial*).tw. (7382)
12. or/9-11 (9977)
13. (exp animal/ or nonhuman/) not exp human/ (6147352)
14. 12 not 13 (9912)
15. limit 14 to yr="2007 -Current" (8530)

Supplementary Table 3: Journals where N=40 CRTs included in the review were published

Acta Paediatrica (1)
Am J Trop Med Hyg (1)
BMC Pregnancy and Childbirth (1)
Br J Psychiatry (1)
Circulation (1)
Clinical Infectious Diseases (1)
East African Medical Journal (1)
Headache (1)
Infection Control and Hospital Epidemiology (1)
JAMA (2)
Journal of Clinical Nursing (1)
Lancet (8)
Malaria (1)
NEJM (7)
PLOS Medicine (3)
PLOS Neglected Tropical Diseases (2)
PLOS ONE (2)
Pediatrics (1)
Sexually transmitted diseases (1)
The Journal of Infectious Diseases (1)
Vaccine (2)

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