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Systematic scoping review of cluster randomised trials conducted exclusively in low-income and middle-income countries between 2017 and 2022

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ABSTRACT

Objective Cluster randomised trials (CRTs) are used for evaluating health-related interventions in low-income and middle-income countries (LMICs) but raise complex ethical issues. To inform the development of future ethics guidance, we aim to characterise CRTs conducted exclusively in LMICs by examining the types of clusters, settings, author affiliations and primary clinical focus and to evaluate adherence to trial registration and ethics reporting requirements over time.

Design A systematic scoping review using the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews.

Data sources We searched MEDLINE between 1 January 2017 and 17 August 2022.

Eligibility criteria for selecting studies We included primary reports of CRTs evaluating health-related interventions, conducted exclusively in LMICs and published in English between 2017 and 2022.

Data extraction and synthesis Data were extracted by one reviewer; a second reviewer verified accuracy by extracting data from 10% of the reports. Results were summarised overall and categorised by country's economic level or publication year.

Results Among 800 identified CRTs, 400 (50.0%) randomised geographical areas and 373 (46.6%) were conducted in Africa. 30 (3.7%) had no authors with an LMIC affiliation, and 246 (30.8%) had neither first nor last author with an LMIC affiliation. The relative frequency of first or last authors holding an LMIC affiliation increases as a country's economic level increases. Most CRTs focused on reducing maternal and neonatal disorders (106, 13.3%). 670 (83.8%) CRTs reported trial registration, 786 (98.2%) reported research ethics committee review and 757 (94.6%) reported consent statements. Among the 757 CRTs, 46 (6.1%) reported a waiver or no consent and, among these, 10 (21.7%) did not provide a rationale. Gatekeepers were identified in 403 (50.4%) CRTs. No meaningful trends were observed in adherence to trial registration or ethics reporting requirements over time.

Conclusion Our findings suggest existing inequity in authorship practices. There is high adherence to trial registration and ethics reporting requirements, although greater attention to reporting a justification for using a waiver of consent is needed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the largest review of cluster randomised trials (CRTs) to date and it provides a comprehensive overview of CRTs conducted exclusively in low-income and middle-income countries.
⇒ We used the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews to report our methods and results.
⇒ Stratifying results allowed for comparison across low-income, lower-middle-income and upper-middle-income country categories.
⇒ Our search was limited to MEDLINE and the English language and using other databases and languages may have identified additional trials but our substantive conclusions would likely not have changed.
⇒ Single data extraction was used, although there was high inter-reviewer agreement on a subset of 80 trials used to ensure accuracy and consistency of data extraction.

INTRODUCTION

Cluster randomised trials (CRTs) are an important research design for evaluating interventions to address acute and chronic health and public health issues.[1] As opposed to individually randomised trials that randomly allocate individuals to study interventions, CRTs randomly allocate groups of people or 'clusters' to study interventions. CRT designs are often used when the intervention must be delivered to a group rather than an individual (eg, vector control interventions), when evaluating the direct and indirect effects of interventions such as vaccines, and when there is substantial risk of spillover effects across study

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arms resulting in attenuation of intervention effects. These designs might also be particularly useful in low-income and middle-income counties (LMICs), as they offer logistical and practical advantages over individual randomisation, such as facilitating the fieldwork and intervention delivery across large geographical areas and lowering implementation costs.[2]

Besides the well-documented methodological issues with CRTs, such as their statistical inefficiency and increased risks of bias compared with individually randomised trials,[3–8] these trials raise complex ethical issues.[9] The *Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials*—the most comprehensive international ethics guidance document specific to CRTs—proffers 15 recommendations to address ethical issues raised by CRTs (see online supplemental table 1 for *Ottawa Statement* recommendations).[10]

One of the recognised limitations of the *Ottawa Statement* is the under-representation of LMIC perspectives. The authors 'recommend that subsequent versions include greater LMIC representation,'[10] and, since its publication, various efforts have focused on greater collaboration with LMIC representatives to identify issues specific to CRTs in LMICs in need of further guidance.[1 11–14] To further assist with the identification of unique ethical and methodological issues and inform the forthcoming update of the *Ottawa Statement*, we conducted a systematic scoping review to describe CRTs in LMICs and create a database of trials that can serve as a rich resource for further in-depth analyses. Specific objectives are: (1) to characterise the types of clusters, settings, author affiliations and primary clinical focus of CRTs in LMICs; (2) to describe adherence to trial registration and ethics reporting requirements—specifically the *Ottawa Statement* recommendations on research ethics committee review, informed consent and gatekeeping; and (3) to explore variations across income strata and over time.

METHODS

We report our methods and results according to the Preferred Reporting Items for Systematic Review and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR).[15] Our PRISMA-ScR checklist is available in online supplemental table 2.

Search strategy

Our search filter (shown in online supplemental table 3) was adapted from a search used in a previously published systematic review of CRTs evaluating public health interventions in LMICs.[16] The adaptation involved removing public health terms, adding the names of LMICs (as of 16 August 2023), and, for efficiency, superimposing the Cochrane Highly Sensitive Search Strategy for identifying randomised controlled trials.[17] We implemented the search in MEDLINE to identify trials published between 1 January 2017 and 17 August 2022 (the date of the search). We limited our search to MEDLINE, which was considered suitable for capturing a large, representative sample of CRTs in LMICs. We chose 1 January 2017 as the start date because this marks about 5 years since the publication of the *Ottawa Statement*, providing ample opportunity for the dissemination of and adherence to ethics guidance and reporting requirements.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (1) published in English language, (2) primary reports of CRTs, (3) evaluated health-related interventions and (4) conducted exclusively in LMICs, classified by the World Bank as low-income, lower-middle-income or upper-middle-income countries.[18] Primary reports were defined as presenting the primary outcomes of the trial. Our strategy for identifying primary reports is reported elsewhere.[19] Health-related interventions were defined as health, healthcare or public health interventions or implementation strategies. Studies were excluded if they met any of the following criteria: (1) no human participants or evaluated a medical education intervention with simulated patients; (2) clusters were households, dyads or families; (3) clusters were individuals with measures on multiple body parts; (4) there was further random or non-random allocation of participants within randomised clusters; or (5) described a study within a trial. Conference abstracts, design papers, editorials, protocols or design papers, pilot and feasibility studies, secondary analyses and process evaluations were also excluded. The full list of inclusion and exclusion criteria is available in online supplemental table 4.

Study selection

All identified records were uploaded into Covidence software.[20] Title and abstract screening of each record was completed independently by two of four reviewers (AS, CEG, MT and YM) with discrepancies being resolved during regular consensus meetings. Six reviewers (AS, CEG, JFS, LQ, MT and YM) proceeded with full-text screening of all potentially eligible studies, with two independent reviewers screening each record and discrepancies being resolved during regular consensus meetings.

Data extraction

A data extraction form was developed and then pilot tested by 3 reviewers (CEG, MT and YM) using 25 randomly selected eligible records. The final extraction form was uploaded into Covidence software. The form is available in online supplemental table 5. One reviewer (YM) proceeded to extract data from all records, while a second reviewer (CEG) extracted data from 80 records in batches of 10 or 15 records every 2 weeks over 12 weeks to ensure accurate and consistent data extraction. If differences could not be resolved between reviewers, a third reviewer (MT) was considered the final arbitrator.

To address objective 1 (characterise the types of clusters, settings, author affiliations and primary clinical focus of CRTs in LMICs), data were extracted on

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type of CRT design (eg, crossover, factorial, parallel arm, stepped wedge), type of cluster (eg, primary care clinics or settings, hospitals or specialised care settings, geographical areas) and country or countries of trial conduct. We reviewed authors' affiliations to determine whether authors of the primary CRT report held LMIC affiliations, and whether first and last authors were affiliated with high-income country institutions, LMIC institutions or both. We recorded detailed information about the primary focus of each CRT using the Institute for Health Metrics and Evaluation's Global Burden of Disease 2019 Cause and Risk Summaries.[21] We classified the stated primary trial objective in each CRT into one of the three Global Burden of Disease Level I categories; namely, whether the primary objective was (1) to reduce the prevalence or incidence of a disease of health problem, (2) to reduce or prevent health risks or (3) to manage impairments. Trials that could not be classified as (1), (2) or (3) were classified as 'other'. Within each level 1 category, we selected the most relevant level 2 and level 3 subcategories from a drop-down list.

To address objective 2 (examine adherence to trial registration and ethics reporting requirements), data were extracted on whether trials were reported to be registered anywhere in the abstract or full text and, if so, in which trial registries. We extracted whether the study reported research ethics committee approval, exemption or non-submission, and justifications for receiving an exemption from or not submitting a protocol for research ethics committee review. If research ethics committee approval was obtained, we documented the location of the research ethics committee (ie, host country, sponsor county or both). We identified whether a clear statement about participant informed consent was reported. If reported, we extracted from whom consent was obtained (ie, individual-level participants or professional-level participants) or if consent was waived or otherwise not obtained. If consent was reported as waived or otherwise not obtained, any justifications or rationales provided were documented and subsequently categorised. We extracted information on whether a gatekeeper had a reported role and, if so, we documented and post hoc categorised their role in the trial by inductive analysis.

Data analysis

A descriptive analysis was used to summarise results using frequencies and percentages for all categorical variables, and medians and interquartile ranges for continuous variables with skewed distributions. Results were presented overall and stratified by World Bank classifications (ie, low income, lower-middle income, upper-middle income) and publication year (2017–2018, 2019–2020, 2021–2022). For all our analyses, we used R (V.4.3.1).

Patient and public involvement

Patients and members of the public were not involved in the design, conduct, reporting or dissemination plans of this study.

RESULTS

Our search strategy identified 3381 records. After duplicates were removed, 3355 records underwent title and abstract screening. Inter-rater agreement on which studies met the criteria for full-text screening was high (raw percentage agreement 87.4%; kappa statistic 0.83, 95% CI: 0.91 to 1.00) and resulted in 2226 records being excluded. After full-text screening of the remaining 1129 records, 800 CRTs were included in our review. The study flow diagram is presented in figure 1.

Trial characteristics

Types of CRT designs included parallel arm (716, 89.5%), stepped wedge (45, 5.6%), factorial (30, 3.8%), crossover (8, 1.0%) and parallel adaptive (1, 0.1%). Clusters were most commonly geographical areas (400, 50.0%), primary care clinics or settings (167, 20.9%) and schools or classrooms (110, 13.8%). The three countries in which most CRTs were conducted were India (83, 10.4%), China (78, 9.8%) and Kenya (53, 6.6%). Table 1 presents descriptive characteristics of the 800 CRTs included in our review, online supplemental table 6 presents a full breakdown of CRT conduct by country.

Among 800 CRTs, 30 (3.7%) had no authors affiliated with an institution based in an LMIC, while 124 (15.5%) were published by authors who were all affiliated with an institution based in an LMIC. First author affiliations were exclusively within high-income countries in 338 (42.2%) CRTs, exclusively with LMICs in 336 (42.0%) and both high-income country and LMIC affiliations in 126 (15.8%). Last author affiliations were exclusively with high-income countries in 410 (51.2%) CRTs, exclusively with LMICs in 303 (37.9%) and both high-income country and LMIC affiliations in 87 (10.9%). The prevalence of first and last author LMIC affiliation increases as country's economic level increases. In 246 (30.8%) CRTs, neither first nor last author had an LMIC affiliation. Table 2 provides the descriptive summary of author affiliations.

The most commonly reported primary focus among the 800 CRTs was maternal and neonatal disorders (106, 13.3%), followed by HIV/AIDS and other sexually transmitted infections (91, 11.4%) and malaria and other neglected tropical diseases (88, 11.0%). Figure 2 presents the top 10 primary foci of CRTs in LMICs. Online supplemental table 7 presents a frequency distribution of the primary focus of each CRT, including the Global Burden of Disease level 1, 2 and level 3 categories.[21]

Trial registration and ethics reporting

Table 3 presents information relevant to trial registration and ethics reporting. Among 800 CRTs, 670 (83.8%)

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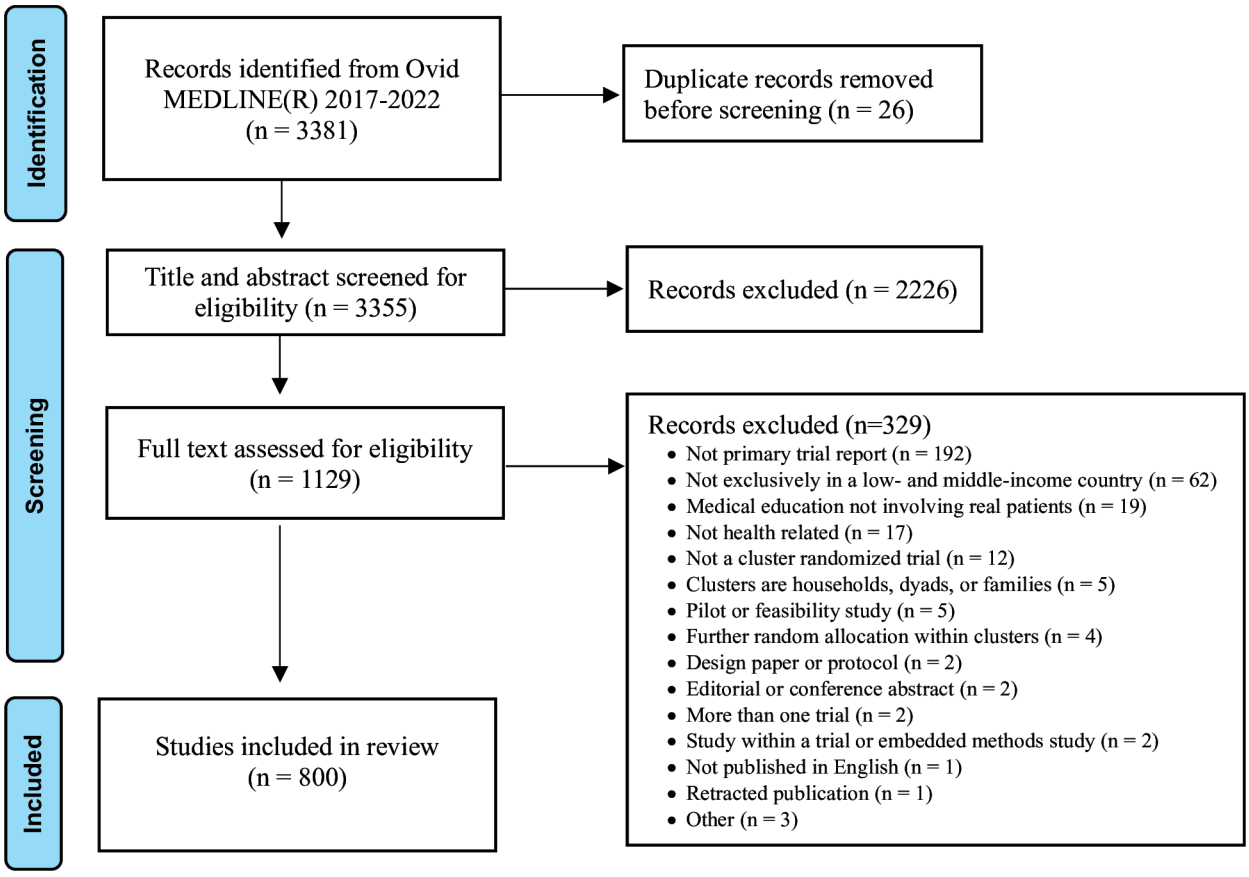

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

reported registration in 19 different trial registries. Among the 670 CRTs reporting registration, 642 (95.8%) reported registration in one registry and 28 (4.2%) in two different registries.

A statement about research ethics committee approval was reported in 786 (98.1%) CRTs. Of these, 452 (57.5%) reported review from both host and sponsor country, 315 (40.1%) from host country only, 18 (2.3%) from sponsor country only and 1 (0.1%) reported review from a for-profit ethics committee not associated with either the host or sponsor country.

A statement about consent was reported in 757 (94.6%) CRTs. Among studies with a consent statement, 683 (90.2%) pertained to individual-level participants (eg, patients, students), 56 (7.4%) pertained to professional-level participants (eg, health providers, teachers), 16 (2.1%) pertained to both individual-level and professional-level participants and 2 (0.3%) were unclear.

Informed consent was reported as being obtained for all aspects of the trial in 711 (93.9%) CRTs, obtained for only some aspects of the trial (eg, data collection procedures) in 20 (2.7%) and not obtained or waived for all aspects of the trial in 25 (3.3%). One (0.1%) CRT reported obtaining written informed consent from participants enrolled at three study sites, while a waiver of consent was granted at 30 study sites.

For CRTs in which consent was not obtained or waived for some or all aspects of the trial, 36 (78.3%) provided a rationale. Rationales included the use of deidentified routinely collected data, administrative data or registry data (23, 63.9%), the research involves a standard of care or usual care intervention (6, 17.7%), consent was obtained from gatekeepers (4, 11.1%), the research involves a cluster-level intervention (3, 8.3%) and other (14, 38.9%).

A gatekeeper's role was identified in 403 (50.4%) CRTs. Identified gatekeeper roles included: assisting with study implementation or intervention development; facilitating or involved in consultations, engagement activities or public events; identifying eligible clusters or participants; providing or withholding access to data or study intervention(s); providing or withholding permission for study conduct or to approach cluster members; providing proxy consent on behalf of cluster members; and reviewing or approving study protocols.

No meaningful changes over time were observed with respect to reporting of trial registration or consent.

DISCUSSION

Summary of key findings

This systematic scoping review characterises the types of clusters, settings, author affiliations and primary clinical focus of CRTs in LMICs. Geographical areas were the most common units of randomisation. We found that most CRTs were conducted in India, China and Kenya. Almost

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Table 1 Descriptive characteristics of n=800 cluster randomised trials included in the review

	Frequency (%)			
	Exclusively low-income countries	Exclusively lower-middle-income countries	Exclusively upper-middle-income countries	Total*
	N=183	N=397	N=210	N=800
Publication year				
2017	34 (18.6)	54 (13.6)	33 (15.7)	121 (15.1)
2018	26 (14.2)	48 (12.1)	32 (15.2)	108 (13.5)
2019	33 (18.0)	77 (19.4)	34 (16.2)	148 (18.5)
2020	33 (18.0)	74 (18.6)	42 (20.0)	151 (19.0)
2021	47 (25.7)	91 (22.9)	38 (18.1)	177 (22.1)
2022	10 (5.46)	53 (13.3)	31 (14.8)	95 (11.8)
Trial design				
Parallel arm	165 (90.2)	353 (88.9)	189 (90.0)	716 (89.5)
Stepped wedge	10 (5.46)	21 (5.3)	12 (5.7)	45 (5.6)
Factorial	7 (3.8)	17 (4.3)	7 (3.3)	30 (3.8)
Crossover	0 (0.0)	6 (1.5)	2 (1.0)	8 (1.0)
Parallel adaptive	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Unit of randomisation				
Geographical areas	102 (55.7)	228 (57.4)	64 (30.5)	400 (50.0)
Primary care clinics/ settings	49 (26.8)	72 (18.1)	43 (20.5)	167 (20.9)
Schools/classrooms	8 (4.4)	54 (13.6)	48 (22.9)	110 (13.8)
Hospitals or specialised care settings	4 (2.2)	19 (4.8)	26 (12.4)	50 (6.3)
Professionals	4 (2.2)	1 (0.3)	9 (4.3)	14 (1.8)
Workplaces	0 (0.0)	3 (0.8)	8 (3.8)	11 (1.4)
Childcare institutions	2 (1.1)	1 (0.3)	5 (2.4)	8 (1.0)
Residential complexes	1 (0.5)	4 (1.0)	1 (0.5)	6 (0.8)
Mixed units of randomisation	2 (1.1)	5 (1.3)	1 (0.5)	8 (1.0)
Other†	11 (6.0)	10 (2.5)	5 (2.4)	26 (3.25)
WHO region of trial conduct				
Africa	181 (98.9)	155 (39.0)	37 (17.6)	373 (46.6)
South-East Asia	0 (0.0)	160 (40.3)	15 (7.1)	175 (21.9)
Western Pacific	0 (0.0)	29 (7.3)	88 (41.9)	117 (14.6)
Americas	0 (0.0)	2 (0.5)	63 (30.0)	65 (8.1)
Eastern Mediterranean	2 (1.1)	50 (12.6)	1 (0.5)	53 (6.6)
Europe	0 (0.0)	0 (0.0)	5 (2.4)	5 (0.6)
Multiregional	0 (0.0)	1 (0.3)	1 (0.5)	12 (1.5)

*N=10 were multinational cluster randomised trials conducted in mixed economies, for example, both low-income and lower-middle-income countries.
†Other units of randomisation include: days of the week or time of clinic presentation; caregivers and their children; individual with an illness and their close contacts; microfinance loan groups; nursing homes or long-term care facilities; orphanages; pharmacies or dispensaries; places of worship; prisons; recreational community clubs; and support groups.

all CRTs included at least one author with an LMIC affiliation, but a substantial minority had neither first nor last author with an LMIC affiliation. We also found that the relative frequency of all authors having exclusively LMIC affiliations increases as a country's economic level increases and that the prevalence of the first or last author having exclusively LMIC affiliations increases as a country's economic level increases. The most common

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Table 2 Overview of author affiliations among n=800 cluster randomised trials included in the review

	Frequency (%)			
	Exclusively low-income countries	Exclusively lower-middle-income countries	Exclusively upper-middle-income countries	Total*
	N=183	N=397	N=210	N=800
Was at least one author affiliated with an LMIC?				
Yes	175 (95.6)	379 (95.5)	206 (98.1)	770 (96.3)
No	8 (4.4)	18 (4.5)	4 (1.9)	30 (3.7)
Were all authors affiliated with an LMIC?				
Yes	13 (7.1)	55 (13.9)	56 (26.7)	124 (15.5)
No	170 (89.9)	342 (86.1)	154 (73.3)	676 (84.5)
What was the first author's affiliation?				
Exclusively HIC	95 (51.9)	185 (46.6)	51 (24.3)	338 (42.2)
Exclusively LMIC	52 (28.4)	147 (37.0)	134 (63.8)	336 (42.0)
Joint HIC and LMIC	36 (19.7)	65 (16.4)	25 (11.9)	126 (15.8)
What was the last author's affiliation?				
Exclusively HIC	109 (59.6)	226 (56.9)	66 (31.4)	410 (51.2)
Exclusively LMIC	54 (29.5)	129 (32.5)	120 (57.1)	303 (37.9)
Joint HIC and LMIC	20 (10.9)	42 (10.6)	24 (11.4)	87 (10.9)
Was either the first or last author affiliated with an LMIC?				
Yes	119 (65.0)	255 (64.2)	176 (83.8)	554 (69.2)
No	64 (35.0)	142 (35.8)	34 (16.2)	246 (30.8)

*N=10 were multinational cluster randomised trials conducted in mixed economies, for example, both low-income and lower-middle-income countries.
HIC, high-income country; LMIC, low-income and middle-income country.

primary clinical focus of CRTs in LMICs were to reduce the prevalence or incidence of maternal and neonatal disorders, HIV/AIDS and other sexually transmitted diseases and malaria or other neglected tropical diseases.

We found that most CRTs in LMICs report trial registration. We also found that adherence to ethics recommendations was high, although not ideal. Nearly all CRTs report a statement about research ethics committee

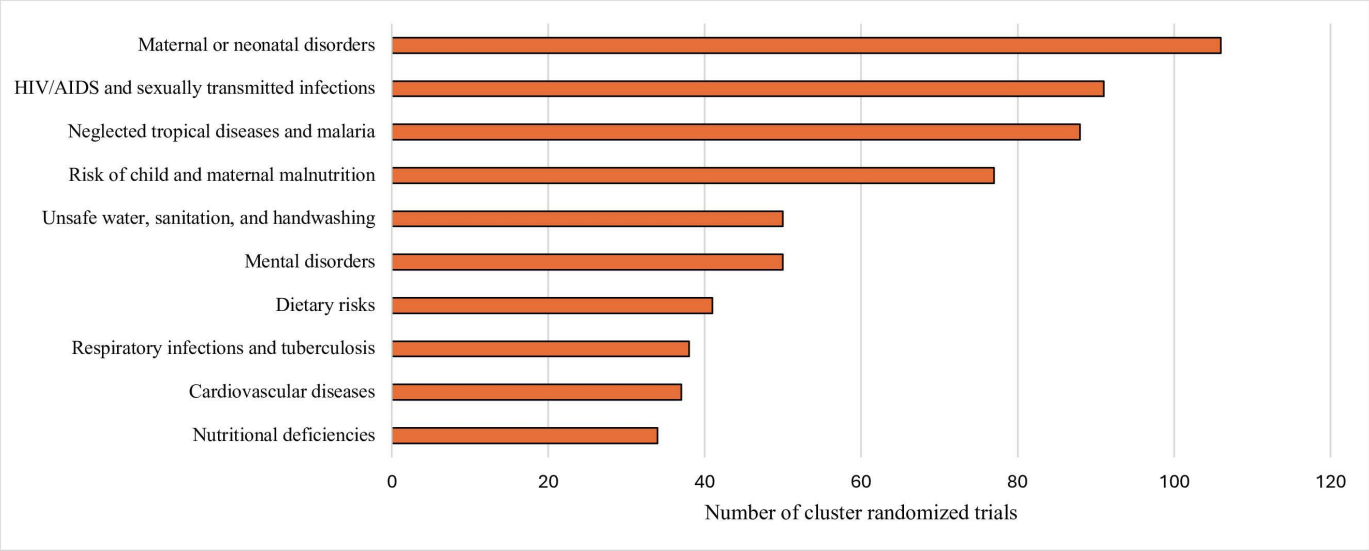

Figure 2 Top 10 primary clinical focus of n=800 cluster randomised trials in low-income and middle-income countries.* Categories taken from the Institute for Health Metrics and Evaluation's Global Burden of Disease 2019 Cause and Risk Summaries.

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Table 3 Adherence to trial registration and ethics reporting requirements in n=800 cluster randomised trials included in the review

	Frequency (%)			
	2017–2018	2019–2020	2021–2022	Total*
	N=229	N=299	N=272	N=800
Was trial registration reported?†				
Yes	190 (83.0)	254 (84.9)	226 (83.1)	670 (83.8)
No	39 (17.0)	45 (15.1)	46 (16.9)	130 (16.2)
Number of registries reported				N=670
One	181 (95.3)	240 (94.5)	220 (97.3)	641 (95.6)
Two	9 (4.7)	14 (5.5)	6 (2.7)	29 (4.4)
Was a statement about research ethics committee review reported?				
Yes, reported REC approval	222 (96.9)	295 (98.7)	269 (98.9)	786 (98.2)
Yes, reported REC exemption	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Yes, reported not submitted for REC review	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	7 (3.1)	4 (1.3)	3 (1.1)	14 (1.8)
Where was the REC located?				N=786
Both host and sponsor country	136 (61.3)	175 (59.3)	142 (52.8)	452 (57.5)
Host country only	79 (35.6)	113 (38.3)	122 (45.4)	315 (40.1)
Sponsor country only	7 (3.2)	6 (2.0)	5 (1.9)	18 (2.3)
Neither host nor sponsor country‡	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Was a statement about consent provided?				
Yes	215 (93.9)	288 (96.3)	254 (93.4)	757 (94.6)
No	14 (6.1)	11 (3.7)	18 (6.6)	43 (5.4)
To whom did the statement about consent pertain?				N=757
Individual-level participants	197 (91.6)	261 (90.6)	225 (88.6)	683 (90.2)
Both individual-level and professional-level participants	16 (7.4)	18 (6.2)	22 (8.7)	56 (7.4)
Professional-level participants	2 (0.9)	7 (2.4)	7 (2.8)	16 (2.1)
Unclear§	0 (0.0)	2 (0.7)	0 (0.0)	2 (0.3)
Was informed consent obtained or not for some or all aspects of the trial?				N=757
Yes, consent was obtained for all aspects of the trial	202 (94.0)	268 (93.1)	241 (94.9)	711 (93.9)
No, a waiver of consent was granted or no consent obtained	7 (3.3)	13 (4.5)	5 (2.0)	25 (3.3)
Yes, consent was obtained for some aspects of the trial	6 (2.8)	6 (2.1)	8 (3.1)	20 (2.7)
Other¶	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Was a rationale for not obtaining consent or a waiver of consent provided?				N=46
Yes	10 (76.9	15 (75.0)	11 (84.6)	36 (78.3)
No	3 (23.1)	5 (25.0)	2 (15.4)	10 (21.7)
What was the rationale for not obtaining consent or the waiver of consent?**				N=36
Trial only uses deidentified, routinely collected data	5 (50.0)	8 (53.3)	4 (36.4)	17 (47.2)
Trial only uses anonymised data (eg, administrative databases, registries)	2 (20.0)	4 (26.7)	5 (45.5)	11 (30.6)

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Table 3 Continued

	Frequency (%)			
Trial involves usual care or standard of care treatments	2 (20.0)	3 (20.0)	1 (9.1)	6 (16.7)
Trial is evaluating a cluster-level intervention	0 (0.0)	2 (13.3)	1 (9.1)	3 (8.3)
Trial poses no more than minimal risk	1 (10.0)	0 (0.0)	1 (9.1)	2 (5.6)
Trial would be infeasible with informed consent	0 (0.0)	1 (6.67)	1 (9.1)	2 (5.6)
Trial has important social value	0 (0.0)	1 (6.67)	0 (0.0)	1 (2.8)
Other††	3 (30.0)	6 (40.0)	3 (27.3)	12 (33.3)
Was a gatekeeper role reported in the trial?				
Yes	127 (55.5)	150 (50.2)	126 (46.3)	403 (50.4)
No	92 (40.2)	124 (41.5)	134 (49.3)	350 (43.7)
Unclear‡‡	10 (4.4)	25 (8.4)	12 (4.4)	47 (5.9)

*N=10 were multinational cluster randomised trials conducted in mixed economies, for example, both low-income and lower-middle-income countries.
†The three most common trial registries were ClinicalTrials.gov (NCT), International Standard Randomised Controlled Trial Number and Pan African Clinical Trial Registry.
‡For-profit research ethics committee not associated with the host or sponsor countries.
§Unclear statements of consent referred to consent without specifying from whom consent was obtained.
¶A waiver of consent was granted for all aspects of the trial at 30 sites, while written informed consent was required for all aspects of the trial at three sites.
**Multiple rationales for not obtaining consent or waiving consent are possible; frequencies do not add up to 100%.
††Consent was obtained from a gatekeeper; consent from parents/legal guardian is not required when obtained from minors; consent would preclude large numbers of eligible participants; consent would introduce bias; health providers have a duty to participate in research; trial is evaluating a quality improvement intervention; trial is observing public behaviour; trial does not involve a biomedical intervention; and trial uses cluster randomisation.
‡‡Unclear statements include, for example, 'clinics agreeing to participate'. No gatekeeper is clearly identified in such statements, but a gatekeeper role is clearly identified.
REC, research ethics committee.

review and approval. Almost all CRTs reported a statement about consent and, when reported, it was almost always clear from whom consent was obtained. However, when consent was reported as not obtained or waived, a substantial minority of CRTs did not report a justification. Many of the provided justifications were not consistent with or explicitly rejected by the *Ottawa Statement* recommendations.

Implications of key findings

One of the most common justifications for adopting a CRT design over an individually randomised design is to avoid contamination between study arms.[22] When geographical areas are selected as the unit of randomisation—which we found to be typical of CRTs in LMICs—there is often a substantial risk of spillover effects caused by migration of individuals between clusters that can undermine the scientific validity of a CRT. Future in-depth analyses should explore any efforts to avoid or mitigate contamination between geographical clusters in these trials.

First and last authorship positions are considered prestigious and are often used by funding agencies reviewing grants and by institutions evaluating applications for promotion. Yet, researchers affiliated with LMIC institutions are often 'stuck in the middle when it comes to global health authorship resulting from international partnerships'.[23] Our findings suggest that this holds true for many CRTs in LMICs. To take steps towards rectifying inequities in authorship, researchers affiliated with high-income-country institutions should, at the very least, create more opportunities for local LMIC-affiliated collaborators to contribute to CRTs in ways that lead to first and last authorship.[24]

The primary focus of CRTs in LMICs are oriented towards communicable, maternal, neonatal and nutritional diseases, which corresponds to the focus of the global donor community during the Millennium Development Goals period (2000–2015).[25] Since we did not explore this issue in our data, we can only speculate that many of these studies are donor driven. Priorities should evolve, if they have not started to do so already, to address the 'rapid rise in non-communicable diseases and disabilities' that currently account for much of the burden of disease worldwide (with the exception of countries early in the epidemiological transition).[26] The focus of future CRTs in LMICs should correspond to local burden of disease that are of national importance in the Sustainable Development Goals period (2016–2030).[27]

Finally, almost all CRTs in LMICs were compliant with trial registration and ethics reporting recommendations. Yet, there is room for improved reporting of justifications

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for not obtaining consent or using a waiver of consent. A probable reason for poor reporting is that it is not required by most journals or trial reporting guidelines. However, the Consolidated Standards of Reporting Trials extension for stepped-wedge CRTs states, 'When a waiver or modification of consent has been granted by a research ethics committee, it should be reported and a justification given. It should be clear whose consent was waived and whether the waiver pertains to study participation, data collection or both'.[28] Other reporting guidelines ought to be updated to improve reporting of consent practices in CRTs.

Comparison with other studies

This is the first study to describe the characteristics of CRTs conducted exclusively in LMICs. Two previous studies have also examined the characteristics of CRTs and ethics reporting, although none is specific to LMICs: a review of 300 primary CRT reports published between 2000 and 2008[29]; and a review of 173 articles reporting primary or secondary analysis of CRTs published in 2008.[30] These reviews found that 15%–25% of CRTs are conducted in LMICs. Consistent with our findings, these reviews also found that geographical areas are commonly the units of randomization in CRTs; yet, CRTs in LMICs are more likely to randomise geographical areas (50%) than CRTs in general (15%).[29]

In terms of trial registration requirements, Odutayo *et al*'s cross-sectional study of 1122 primary reports of randomised controlled trials published in December 2012 found that only 593 (52.9%) reported trial registration.[31] Among the 1122 trials, 31 (2.8%) were CRTs and, of these, 17 (54.8%) reported trial registration. Our review suggests that CRTs in LMICs are more likely to report trial registration in the primary report than randomised controlled trials and CRTs in general or that a substantial improvement in trial registration has occurred over the last 10 years.

Finally, in terms of ethics reporting, the two aforementioned reviews found that 73%–90% of CRTs include a statement about research ethics committee approval and 69%–83% include a statement about informed consent.[29 30] Compared with these earlier reviews, our review found a higher percentage of reporting research ethics committee approval (98.2%) and informed consent (94.6%), which suggests that adherence to ethics reporting requirements may be higher in CRTs conducted exclusively in LMICs or that an improvement has occurred over time.

Strengths and limitations

Our study is the largest review of CRTs conducted to date and provides a comprehensive overview of CRTs in LMICs. It has also created a large database of CRTs that can serve as a rich recourse for further in-depth analysis. Our study has some limitations. First, by excluding CRTs conducted in high-income countries from the search and only included trials conducted exclusively in LMICs, we cannot compare the two sets of trials. This limits our ability to accurately identify ethical issues that are unique to trials conducted in LMICs. However, stratifying results allowed for some comparison between LMIC categories. Second, our literature search was limited to MEDLINE and the English language; using other databases and languages may have identified additional trials. However, since our study objectives relate to a general characterisation of CRTs conducted in LMICs and a description of their adherence to trial registration and ethics reporting requirements, capturing a large, representative sample of such trials was considered adequate. Searching other databases and including non-English primary reports of CRTs would have been unlikely to yield substantively different conclusions. Third, single data extraction was used since the scope of this review would render duplicate review unmanageable. To limit misclassification, the primary extractor underwent multiple rounds of training prior to commencing data extraction and the extraction form provided clear guidance and examples. There was also high inter-reviewer agreement on the subset of 80 trials that were used to ensure accuracy and consistency of data extraction.

CONCLUSION

In this review, which is part of a larger project to update the *Ottawa Statement*, we compiled a large database of 800 CRTs conducted exclusively in LMICs, characterised the types of clusters, settings, author affiliations and primary clinical focus of these trials and evaluated their adherence to trial registration and ethics reporting requirements. Our findings suggest existing inequity in authorship practices. We also found high adherence to trial registration and ethics reporting requirements, although greater attention to reporting a justification for using a waiver of consent is needed. Future secondary analyses will examine specific ethical and methodological issues in more detail to ensure that the updated *Ottawa Statement* recommendations are applicable to all CRTs irrespective of location, while also providing recommendations to address unique issues raised by CRTs in LMICs.

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Supplementary Table 1: The *Ottawa Statement* recommendations.

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

Supplementary Table 2: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	N/A
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	3-5
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	5-6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	N/A
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	7
Information sources	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	7
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	31-32
Selection of sources of evidence	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	7
Data charting process	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	8-9
Critical appraisal of individual sources of evidence	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	10
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	7
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	8-9
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	10-13
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	10-13
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	13-17
Limitations	20	Discuss the limitations of the scoping review process.	17-18
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	18
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	10, 19

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMAScR): Checklist and Explanation. *Ann Intern Med*. 2018; 169: 467-473.

Supplementary Table 3: search strategy implemented in Ovid MEDLINE.

Search strategy implemented in Ovid MEDLINE Ovid MEDLINE(R) ALL <1946 to August 16, 2022>. Combination of Pérez et al., Taljaard et al., and the Cochrane highly sensitive search (sensitivity and precision maximizing version) with modifications and update of the LMIC countries according to the 2021 World Bank data. Search date: 17 August 2022.		
#	Search strategy	Results
	Search terms from Pérez et al.	
1	Cluster Analysis/	67852
2	Cluster Analys*.tw,kw,sh	87667
3	(communit* adj2 random* adj2 trial*).tw,kw,sh	1000
4	(group adj2 random* adj2 trial*).tw,kw,sh	4263
5	(cluster adj2 random*).tw,kw,sh	19010
6	cluster-random*.tw,kw,sh	16824
7	Or/1-6	108492
	Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format.	
8	randomized controlled trial.pt	575305
9	controlled clinical trial.pt	94992
10	randomized.ab	572552
11	placebo.ab	230932
12	clinical trials as topic.sh	200274
13	randomly.ab	389407
14	trial.ti	268607
15	8 or 9 or 10 or 11 or 12 or 13 or 14	1467384
16	exp animals/ not humans.sh.	5038055
17	15 not 16	1349849
18	17 and 7	**21917**
	Low-income countries	
19	(Afghanistan or Burkina Faso or Burundi or Central African Republic or Chad or Congo or Eritrea or Ethiopia or Gambia or Guinea or Guinea-Bissau or Democratic people's republic of Korea or Liberia or Madagascar or Malawi or Mali or Mozambique or Niger or Rwanda or Sierra Leone or Somalia or South Sudan or Sudan or Syrian Arab Republic or Togo or Uganda or Yemen or Zambia or Developing Countr* or middle income countr* or low income countr*).tw,kw.	353232
20	Afghanistan/ or Burkina Faso/ or Burundi/ or Central African Republic/ or Chad/ or Congo/ or Eritrea/ or Ethiopia/ or Gambia/ or Guinea/ or Guinea-Bissau/ or Democratic people's republic of Korea/ or Liberia/ or Madagascar/ or Malawi/ or Mali/ or Mozambique/ or Niger/ or Rwanda/ or Sierra Leone/ or Somalia/ or South Sudan/ or Sudan/ or Syrian Arab Republic/ or Togo/ or Uganda/ or Yemen/ or Zambia/ or Developing Countries/ or Poverty/ or Rural Population/	253584
	Lower-middle-income countries	
21	(Algeria or Angola or Bangladesh or Benin or Bhutan or Bolivia or Cabo Verde or Cambodia or Cameroon or Comoros or Congo or Cote d'Ivoire or Djibouti or Egypt or El Salvador or Eswatini or Ghana or Haiti or Honduras or India or Indonesia or Iran or Kenya or Kiribati or Kyrgyz or Lao PDR or Lebanon or Lesotho or Mauritania or Micronesia or Mongolia or Morocco or Myanmar or Nepal or Nicaragua or Nigeria or Pakistan or Papua New Guinea or Philippines or American Samoa or Sao Tome or Senegal or Solomon Islands or Sri Lanka or Tajikistan or Tanzania or Timor Leste or Tunisia or Ukraine or Uzbekistan or Vanuatu or Vietnam or Gaza or Zimbabwe).tw,kw.	454194

22	Algeria/ or Angola/ or Bangladesh/ or Benin/ or Bhutan/ or Bolivia/ or Cabo Verde/ or Cambodia/ or Cameroon/ or Comoros/ or Congo/ or Cote d'Ivoire/ or Djibouti/ or Egypt/ or El Salvador/ or Eswatini/ or Ghana/ or Haiti/ or Honduras/ or India/ or Indonesia/ or Iran/ or Kenya/ or Kiribati/ or Kyrgyz/ or Lao PDR/ or Lebanon/ or Lesotho/ or Mauritania/ or Micronesia/ or Mongolia/ or Morocco/ or Myanmar/ or Nepal/ or Nicaragua/ or Nigeria/ or Pakistan/ or Papua New Guinea/ or Philippines/ or American Samoa/ or Sao Tome/ or Senegal/ or Solomon Islands/ or Sri Lanka/ or Tajikistan/ or Tanzania/ or Timor Leste/ or Tunisia/ or Ukraine/ or Uzbekistan/ or Vanuatu/ or Vietnam/ or Gaza/ or Zimbabwe/	416925
	Upper-middle-income countries	
23	(Albania or American Samoa or Argentina or Armenia or Azerbaijan or Belarus or Belize or Bosnia Herzegovina or Botswana or Brazil or Bulgaria or China or Colombia or Costa Rica or Cuba or Dominica or Dominican Republic or Ecuador or Equatorial Guinea or Fiji or Gabon or Georgia or Grenada or Guatemala or Guyana or Iraq or Jamaica or Jordan or Kazakhstan or Kosovo or Libya or Malaysia or Maldives or Marshall Islands or Mauritius or Mexico or Moldova or Montenegro or Namibia or North Macedonia or Palau or Paraguay or Peru or Russia or Serbia or South Africa or St Lucia or St Vincent or Suriname or Thailand or Tonga or Turkiye or Turkey or Turkmenistan or Tuvalu).tw,kw.	659338
24	Albania/ or American Samoa/ or Argentina/ or Armenia/ or Azerbaijan/ or Belarus/ or Belize/ or Bosnia-Herzegovina/ or Botswana/ or Brazil/ or Bulgaria/ or China/ or Colombia/ or Costa Rica/ or Cuba/ or Dominica/ or Dominican Republic/ or Ecuador/ or Equatorial Guinea/ or Fiji/ or Gabon/ or Georgia/ or Grenada/ or Guatemala/ or Guyana/ or Iraq/ or Jamaica/ or Jordan/ or Kazakhstan/ or Kosovo/ or Libya/ or Malaysia/ or Maldives/ or Marshall Islands/ or Mauritius/ or Mexico/ or Moldova/ or Montenegro/ or Namibia/ or North Macedonia/ or Palau/ or Paraguay/ or Peru/ or Russia/ or Serbia/ or South Africa/ or St Lucia/ or St Vincent/ or Suriname/ or Thailand/ or Tonga/ or Turkiye/ or Turkey/ or Turkmenistan/ or Tuvalu/	670947
25	19 or 20 or 21 or 22 or 23 or 24	1827763
26	25 and 18	6096
27	limit 26 to English	5956
28	limit 27 to last 5 years	3381
29	Remove duplicates (within Covidence)	3355

Supplementary Table 4: Eligibility criteria for CRTs in the review.

Inclusion criteria	1. Primary report of a completed cluster randomized trial. 2. Evaluating a health, healthcare, or public health intervention or implementation strategy. 3. Exclusively conducted in low- and middle-income countries. 4. Published in English (for feasibility). 5. Over the past 5 years, i.e., between 1 Jan. 2017 – 16 Aug. 2022 (date of search).
Exclusion criteria	1. Not a primary report of a completed trial, i.e., papers reporting only: baseline findings; preliminary results; subgroup analysis with primary results reported elsewhere; long-term follow-up with primary endpoint reported previously; process evaluation; mediation analysis; sensitivity analysis; or interim analysis. 2. Not a randomized controlled trial. 3. No human participants, e.g., veterinary studies. 4. Individually randomized or individually randomized group treatment trial. 5. Pilot/ feasibility studies. 6. Study protocols/ design papers/ methods papers. 7. Conference abstracts/ editorials. 8. Not evaluating a health, healthcare, or public health intervention or implementation strategy, e.g., evaluating effects of intervention on educational attainment. 9. Medical education trial not involving real patients or patient data, e.g., involves simulated patients, focused on a medical curriculum. 10. Not exclusively conducted in low- and middle-income countries. 11. Not published in English. 12. Clusters are households, dyads, families. 13. Clusters are individuals with measures on multiple body parts, e.g., teeth, eyes, limbs. 14. Further random or non-random allocation of participants within randomized clusters. 15. Study within a trial, e.g., an embedded methods study within a trial to test different consent or recruitment approaches or different types of questionnaires.

Supplementary Table 5: Data abstraction form.

Q1	**Is information about trial registration reported?**						
A	Yes						
B	No (skip Q2 and Q3)						
Q2	**If Q1 = A, select registry name.** *Select all that apply.*						
A	American Economic Association registry (AEARCT)						
B	Australian/ New Zealand clinical trials registry (ANZCTR)						
C	Brazilian clinical trials registry (ReBEC)						
D	Chinese clinical trials registry (CHICTR)						
E	Clinicaltrials.gov (NCT)						
F	Clinical trials registry India (CTRI)						
G	Digital repository (Dryad)						
H	European clinical trials database (EUDRA-CT)						
I	International clinical trials registry platform (ICTRP)						
J	International standard randomized controlled trial number (ISRCTN)						
K	Iranian registry of clinical trials (IRCT)						
L	Pan African clinical trials registry (PACTR)						
M	South African national clinical trials register (SANCTR)						
N	Sri Lanka clinical trials registry (SLCTR)						
O	Thai clinical trial registry (TCTR)						
P	UK clinical research network (UKCRN)						
Q	Other (explain):						
Q3	**If Q1 = A, add registration number(s).**						
A							
B							
C							
Q4	**What is the country or countries of study conduct?** *Select all that apply.*						
A	Afghanistan	Aj	Dominican Republic	Bs	Lebanon	Db	Sao Tome and Principe
B	Albania	Ak	Ecuador	Bt	Lesotho	Dc	Senegal
C	Algeria	Al	Egypt	Bu	Liberia	Dd	Serbia
D	American Samoa	Am	El Salvador	Bv	Libya	De	Sierra Leone
E	Angola	An	Equatorial Guinea	Bw	Madagascar	Df	Solomon Islands
F	Argentina	Ao	Eritrea	Bx	Malawi	Dg	Somalia
G	Armenia	Ap	Eswatini	By	Malaysia	Dh	South Africa
H	Azerbaijan	Aq	Ethiopia	Bz	Maldives	Di	South Sudan
I	Bangladesh	Ar	Fiji	Ca	Mali	Dj	Sri Lanka
J	Belarus	As	Gabon	Cb	Marshall Islands	Dk	St. Lucia
K	Belize	At	Gambia	Cc	Mauritania	Dl	St. Vincent and the Grenadines
L	Benin	Au	Gaza	Cd	Mauritius	Dm	Sudan
M	Bhutan	Av	Georgia	Ce	Mexico	Dn	Suriname
N	Bolivia	Aw	Ghana	Cf	Micronesia	Do	Syrian Arab Republic
O	Bosnia Herzegovina	Ax	Grenada	Cg	Moldova	Dp	Tajikistan
P	Botswana	Ay	Guatemala	Ch	Mongolia	Dq	Tanzania
Q	Brazil	Az	Guinea	Ci	Montenegro	Dr	Thailand
R	Bulgaria	Ba	Guinea-Bissau	Cj	Morocco	Ds	Timor-Leste

S	Burkina Faso	Bb	Guyana	Ck	Mozambique	Dt	Togo
T	Burundi	Bc	Haiti	Cl	Myanmar	Du	Tonga
U	Cabo Verde	Bd	Honduras	Cm	Namibia	Dv	Tunisia
V	Cambodia	Be	Hungary	Cn	Nepal	Dw	Turkiye
W	Cameroon	Bf	India	Co	Nicaragua	Dy	Turkmenistan
X	Central African Republic	Bg	Indonesia	Cp	Niger	Dz	Tuvalu
Y	Chad	Bh	Iran	Cq	Nigeria	Ea	Uganda
Z	China	Bi	Iraq	Cr	North Macedonia	Eb	Ukraine
Aa	Colombia	Bj	Jamaica	Cs	Pakistan	Ec	Uzbekistan
Ab	Comoros	Bk	Jordan	Ct	Palau	Ed	Vanuatu
Ac	Congo, Dem. Rep	Bl	Kazakhstan	Cu	Papua New Guinea	Ee	Vietnam
Ad	Congo, Rep	Bm	Kenya	Cv	Paraguay	Ef	Yemen
Ae	Costa Rica	Bn	Kiribati	Cw	Peru	Eg	Zambia
Af	Cote d'Ivoire	Bo	Korea, DPR	Cx	Philippines	Eh	Zimbabwe
Ag	Cuba	Bp	Kosovo	Cy	Russia	Ei	Other or unclear (explain):
Ah	Djibouti	Bq	Kyrgyz Republic	Cz	Rwanda		
Ai	Dominica	Br	Lao PDR	Da	Samoa		

Q5	**Was at least one author from the country of conduct included in the authorship list?**
A	Yes, all authors are LMIC affiliated
B	Yes, at least one author is LMIC affiliated
C	No, all authors are HIC affiliated
D	Other or unclear (explain)
Q6	**What is the affiliation of the first author?** *If there is joint first authorship, select affiliation of first listed author*
A	Exclusively LMIC
B	Joint LMIC and HIC
C	Exclusively HIC
D	Other or unclear (explain):
Q7	**What is the affiliation of the last author?** *If there is joint last authorship, select affiliation of last listed author.*
A	Exclusively LMIC
B	Joint LMIC and HIC
C	Exclusively HIC
D	Other or unclear (explain):
Q8	**Who was the corresponding author?**
A	First author
B	Last author
C	Other author (e.g., second, third, etc.)
D	Unclear (explain):
Q9	**What is the type of trial design?**
A	Crossover
B	Factorial
C	Parallel arm
D	Stepped wedge
E	Other or unclear (explain):
Q10	**What is the unit of randomization?** *Select all that apply.*
A	Geographical areas (e.g., communities, residential areas, villages)
B	Hospital or specialized care setting
C	Nursing homes or long-term care facilities
D	Primary care clinics or settings
E	Professionals (e.g., health providers, teachers)
F	Schools/classrooms
G	Workplaces
H	Other or unclear (explain):

Q11	**Does the report include a statement about research ethics review?** *Note that "research ethics review" encompasses review by Research Ethics Committees, Research Ethics Boards, Ethical Review Boards, Institutional Review Boards, or other similar committees. It does not include review by Data and Safety Monitoring Boards or Committees.*
A	Yes, reported that the study was approved by a research ethics committee (skip Q12)
B	Yes, reported that the study was submitted but classified as exempt from research ethics committee review
C	Yes, reported that the study was not submitted for research ethics committee review (skip Q13)
D	No statement about research ethics committee review (skip Q12 and Q13)
E	Other or unclear (explain):
Q12	**If Q11 = B or C, what was the justification for lack of research ethics committee review?** *If no justification provided, write "N/A". Otherwise, copy and paste justification.*
Q13	**If Q11 = A or B, where was the research ethics committee located?** *Select all that apply.*
A	Host country
B	Sponsor country
C	Other or unclear (explain):
Q14	**Was a statement about participant informed consent provided in the report?**
A	Yes
B	No (skip Q15-Q17)
C	Other or unclear (explain):
Q15	**If Q14 = A, who provided consent?** *Select all that apply.*
A	Individual-level trial participants (e.g., patients, students, parents on behalf of children) provided consent for at least some aspects of the trial (skip Q16 and Q17)
B	Professional-level trial participants (e.g., health providers, teachers) provided consent for at least some aspects of the trial (skip Q16 and Q17)
C	Waiver of consent or no consent for at least some aspects of the trial
D	Other or unclear (explain):
Q16	**If Q15 = C, was an explanation/ rationale for a waiver of consent or no consent provided?**
A	Yes
B	No (skip Q17)
C	Other of unclear (explain):
Q17	**If Q16 = A, what was the explanation/ rationale for a waiver of consent or no consent?** *Copy and paste relevant text.*
Q18	**Was a gatekeeper involved in the trial?** *Gatekeepers are individuals or groups (e.g., school principal, village chief) who has the authority to protect the interests of a cluster.*
A	Yes (e.g., principals gave permission for their school to participate…"
B	No (skip Q19)
C	Unclear (e.g., "clinics that agreed to participate…")
Q19	**If Q18 = A or B, who was the gatekeeper and what was their role?** *Copy and paste relevant text.*
Q20	**What was the main focus of the trial?** *Testing an intervention to…*
A	Reduce prevalence or incidence of a disease/health problem (go to Q21)
B	Reduce or prevent risk (go to Q25)
C	Manage impairments (go to Q29)
D	Other or unclear (explain):
Q21	**If Q20 = A, what disease or health problem is being studied?** *Select all that apply.*
A	Communicable, maternal, neonatal, and nutritional diseases (go to Q22)
B	Non-communicable diseases (go to Q23)
C	Injuries (go to Q24)
Q22	**If Q21 = A, what communicable, maternal, neonatal, and nutritional disease is being studied?** *Select all that apply. After responding, go to Q30.*
A	HIV/AIDS & sexually transmitted infections
B	Respiratory infections & tuberculosis
C	Enteric infections (e.g., diarrheal diseases, typhoid, intestinal infections)
D	Neglected tropical diseases & malaria (e.g., onchocerciasis, dengue, yellow fever, ebola, zika)
E	Other infectious diseases (e.g., meningitis, encephalitis, diphtheria, tetanus, measles, varicella & herpes zoster)
F	Maternal and neonatal disorders
G	Nutritional deficiencies
Q23	**If Q21 = B, what non-communicable disease is being studied?** *Select all that apply. After responding, go to Q30.*

A	Cardiovascular diseases
B	Neoplasms
C	Other non-communicable
D	Musculoskeletal disorders
E	Mental disorders
F	Diabetes and CKD
G	Chronic respiratory
H	Neurological disorders
I	Digestive diseases
J	Sense organ diseases
K	Skin diseases
Q24	**If Q21 = C, what injury is being studied?** *Select all that apply. After responding, go to Q30.*
A	Transport injuries (e.g., road injuries, motor vehicle accidents)
B	Unintentional injuries (e.g., falls, drowning, fire, poisonings)
C	Self-harm and violence
Q25	**If Q20 = B, what risk factors are being studied?** *Select all that apply.*
A	Environmental or occupational risks (go to Q26)
B	Behavioural risks (go to Q27)
C	Metabolic risks (go to Q28)
Q26	**If Q25 = A, what environmental or occupational risks are being studied?** *Select all that apply. After responding, go to Q30.*
A	Unsafe water, sanitation, and handwashing
B	Air pollution
C	Non-optimal temperature
D	Other environmental risks (e.g., residential radon, lead exposure)
E	Occupational risks (e.g., occupational exposure to carcinogens; occupational injuries; ergonomic factors)
Q27	**If Q25 = B, what behavioural risks are being studied?** *Select all that apply. After responding, go to Q30.*
A	Child and maternal malnutrition
B	Tobacco
C	Alcohol use
D	Drug use
E	Dietary risks
F	Intimate partner violence
G	Childhood sexual abuse and bullying
H	Unsafe sex
I	Low physical activity
Q28	**If Q25 = C, what metabolic risks are being studied?** *Select all that apply. After responding, go to Q30.*
A	High fasting plasma glucose
B	High LDL cholesterol
C	High systolic blood pressure
D	High body-mass index
E	Low bone mineral density
F	Kidney dysfunction
Q29	**If Q20 = C, what impairments are being studied?** *Select all that apply. After responding, go to Q30.*
A	Anemia
B	Epilepsy
C	Guillain-Barré syndrome
D	Hearing loss
E	Heart failure
F	Infertility
G	Developmental intellectual disability
H	Pelvic inflammatory disease
I	Blindness and vision loss

Q30	**Was the trial explicitly labelled as "pragmatic" or "real-world"?**
A	Yes, at least in the title or abstract
B	Yes, in the full text only
C	No
Q31	**Note any comments or concerns.**

Supplementary Table 6: Geographical distribution of N=800 CRT included in the review.

	Frequency (%)
Country*	**N=800**
India	83 (10.4)
China	78 (9.8)
Kenya	53 (6.6)
Ethiopia	48 (6.0)
Uganda	37 (4.6)
South Africa	34 (4.3)
Tanzania	34 (4.3)
Bangladesh	32 (4.0)
Malawi	32 (4.0)
Brazil	27 (3.4)
Ghana	25 (3.1)
Iran	23 (2.9)
Pakistan	23 (2.9)
Indonesia	21 (2.6)
Nepal	20 (2.5)
Nigeria	17 (2.1)
Zimbabwe	17 (2.1)
Burkina Faso	16 (2.0)
Thailand	15 (1.9)
Zambia	15 (1.9)
Peru	11 (1.4)
Vietnam	11 (1.4)
Malaysia	10 (1.3)
Mexico	10 (1.3)
Rwanda	10 (1.3)
Dem. Rep. Congo	8 (1.0)
Niger	8 (1.0)
Cambodia	7 (0.9)
Mozambique	7 (0.9)
Argentina	6 (0.8)
Colombia	6 (0.8)
Sri Lanka	6 (0.8)
Mali	5 (0.7)
Philippines	5 (0.7)
Cote d'Ivoire	4 (0.5)
Guatemala	4 (0.5)
Lao PDR	4 (0.5)
Lesotho	4 (0.5)
Papua New Guinea	4 (0.5)
Sierra Leone	4 (0.5)
The Gambia	4 (0.5)
Botswana	3 (0.4)
Egypt	3 (0.4)
Eswatini	3 (0.4)
Haiti	3 (0.4)
Lebanon	3 (0.4)
Myanmar	3 (0.4)
Senegal	3 (0.4)
Benin	2 (0.3)
Bosnia and Herzegovina	2 (0.3)
Burundi	2 (0.3)
Cameroon	2 (0.3)
Guinea-Bissau	2 (0.3)
Afghanistan	1 (0.1)
Angola	1 (0.1)
Armenia	1 (0.1)
Chad	1 (0.1)
Costa Rica	1 (0.1)
Cuba	1 (0.1)
Ecuador	1 (0.1)
Fiji	1 (0.1)
Guinea	1 (0.1)
Jordan	1 (0.1)
Kazakhstan	1 (0.1)
Kosovo	1 (0.1)
Liberia	1 (0.1)
Madagascar	1 (0.1)
Mongolia	1 (0.1)
Montenegro	1 (0.1)
Morocco	1 (0.1)
Namibia	1 (0.1)
North Macedonia	1 (0.1)
Serbia	1 (0.1)
South Sudan	1 (0.1)
Sudan	1 (0.1)
Timor-Leste	1 (0.1)
Togo	1 (0.1)
Turkiye	1 (0.1)
Albania	0 (0.0)
Algeria	0 (0.0)
American Samoa	0 (0.0)
Azerbaijan	0 (0.0)
Belarus	0 (0.0)
Belize	0 (0.0)
Bhutan	0 (0.0)
Bolivia	0 (0.0)
Bulgaria	0 (0.0)
Central African Republic	0 (0.0)
Comoros	0 (0.0)
Dem. Rep. Korea	0 (0.0)
Djibouti	0 (0.0)
Dominica	0 (0.0)
Dominican Republic	0 (0.0)
El Salvador	0 (0.0)
Equatorial Guinea	0 (0.0)
Eritrea	0 (0.0)
Federated States of Micronesia	0 (0.0)
Gabon	0 (0.0)
Gaza	0 (0.0)
Georgia	0 (0.0)
Grenada	0 (0.0)
Guyana	0 (0.0)
Honduras	0 (0.0)
Iraq	0 (0.0)
Jamaica	0 (0.0)
Kiribati	0 (0.0)
Kyrgyzstan	0 (0.0)
Libya	0 (0.0)
Maldives	0 (0.0)
Marshall Islands	0 (0.0)
Mauritania	0 (0.0)
Mauritius	0 (0.0)
Moldova	0 (0.0)
Nicaragua	0 (0.0)
Palau	0 (0.0)
Paraguay	0 (0.0)
Republic of Cabo Verde	0 (0.0)
Republic of the Congo	0 (0.0)
Russian Federation	0 (0.0)
Saint Lucia	0 (0.0)
Saint Vincent and the Grenadines	0 (0.0)
Samoa	0 (0.0)
São Tomé and Príncipe	0 (0.0)
Solomon Islands	0 (0.0)
Somalia	0 (0.0)
Suriname	0 (0.0)
Syria	0 (0.0)
Tajikistan	0 (0.0)
Tonga	0 (0.0)
Tunisia	0 (0.0)
Turkmenistan	0 (0.0)
Tuvalu	0 (0.0)
Ukraine	0 (0.0)
Uzbekistan	0 (0.0)
Vanuatu	0 (0.0)
Venezuela	0 (0.0)
Yemen	0 (0.0)

* Due to multinational trials, frequencies do not add to 100%.

Supplementary Table 7: Primary clinical focus of N=800 cluster randomized trials included in the review.

	Frequency (%)			
	Exclusively low-income countries	**Exclusively lower-middle income countries**	**Exclusively upper-middle income countries**	**Total[1]**
Primary clinical focus of the trial[2]	**N = 183**	**N = 397**	**N = 210**	**N=800**
To reduce prevalence or incidence of disease and injury	**N = 105**	**N = 239**	**N = 133**	**N=486 (60.8)**
Communicable, maternal, neonatal, and nutritional diseases[3]	95 (90.5)	164 (68.6)	62 (46.6)	330 (67.9)
Maternal and neonatal disorders	26 (27.4)	60 (36.6)	15 (24.2)	106 (32.1)
HIV/AIDS and sexually transmitted infections	30 (31.6)	38 (23.2)	22 (35.5)	91 (27.6)
Neglected tropical diseases and malaria	27 (28.4)	44 (26.8)	16 (25.8)	88 (26.7)
Respiratory infections and tuberculosis	11 (11.6)	15 (9.14)	10 (16.1)	38 (11.5)
Nutritional deficiencies	11 (11.6)	16 (9.76)	10 (16.1)	34 (10.3)
Enteric infections	3 (3.2)	5 (3.0)	0 (0.0)	8 (2.4)
Other infectious diseases[4]	2 (2.1)	1 (0.61)	1 (1.6)	4 (1.2)
Non-communicable diseases[3]	15 (14.3)	86 (36.0)	69 (51.9)	170 (35.0)
Mental disorders	8 (53.3)	26 (30.2)	16 (23.2)	50 (29.4)
Cardiovascular diseases	0 (0.0)	15 (17.4)	22 (31.9)	37 (21.8)
Diabetes and CKD	0 (0.0)	15 (17.4)	15 (21.7)	30 (17.6)
Sense organ diseases	0 (0.0)	8 (9.3)	7 (10.1)	15 (8.8)
Neoplasms	2 (13.3)	5 (5.8)	4 (5.8)	11 (6.5)
Chronic respiratory diseases	0 (0.0)	1 (1.2)	3 (4.3)	4 (2.4)
Musculoskeletal disorders	0 (0.0)	1 (1.2)	3 (4.3)	4 (2.4)
Skin diseases	0 (0.0)	3 (3.5)	0 (0.0)	3 (1.8)
Neurological disorders	1 (6.7)	0 (0.0)	0 (0.0)	1 (0.6)
Other non-communicable diseases[5]	5 (33.3)	18 (20.9)	6 (8.7)	29 (17.1)
Injuries[3]	1 (0.95)	6 (2.5)	4 (3.0)	11 (2.3)
Unintentional injuries	1 (100.0)	6 (100.0)	2 (50.0)	9 (81.8)
Transport injuries	0 (0.0)	0 (0.0)	2 (50.0)	2 (18.2)
Self-harm and violence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
To reduce or prevent risk factors	**N = 64**	**N=131**	**N = 60**	**N=255 (31.9)**
Behavioural risks[3]	49 (76.6)	93 (71.0)	47 (78.3)	189 (74.1)
Child and maternal malnutrition	30 (61.2)	39 (41.9)	6 (12.8)	77 (40.7)
Dietary risks	3 (6.1)	18 (19.4)	15 (31.9)	41 (21.7)
Unsafe sex	11 (28.2)	14 (15.1)	6 (12.8)	31 (16.4)
Low physical activity	0 (0.0)	9 (9.7)	15 (31.9)	30 (15.9)
Tobacco use	4 (8.2)	13 (14.0)	5 (10.6)	20 (10.6)
Intimate partner violence	5 (10.2)	9 (9.7)	4 (8.5)	17 (9.0)
Childhood sexual abuse and bullying	0 (0.0)	6 (6.5)	2 (4.3)	13 (6.9)
Alcohol use	0 (0.0)	4 (4.3)	2 (4.3)	7 (3.7)

Drug use	0 (0.0)	2 (2.2)	2 (4.3)	4 (2.1)
Environmental or occupational risks[3]	17 (26.6)	33 (25.2)	4 (6.7)	54 (21.2)
Unsafe water, sanitation, and handwashing	15 (88.2)	31 (93.9)	2 (50.0)	50 (92.6)
Air pollution	3 (17.6)	2 (6.1)	0 (0.0)	5 (9.3)
Occupational risks	0 (0.0)	0 (0.0)	2 (50.0)	2 (3.7)
Metabolic risks[3]	0 (0.0)	14 (10.7)	19 (31.7)	33 (12.9)
High body-mass index	0 (0.0)	5 (35.7)	13 (68.4)	18 (54.5)
High systolic blood pressure	0 (0.0)	10 (71.4)	7 (36.8)	17 (51.5)
High fasting plasma glucose	0 (0.0)	6 (42.9)	1 (5.3)	7 (21.2)
High LDL cholesterol	0 (0.0)	3 (21.4)	2 (10.5)	5 (15.2)
Low bone mineral density	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Kidney disfunction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
To manage impairments	**N = 1**	**N = 4**	**N = 0**	**N=5 (0.6)**
Developmental intellectual disability	0 (0.0)	3 (75.0)	0 (0.0)	3 (60.0)
Anemia	1 (100.0)	0 (0.0)	0 (0.0)	1 (20.0)
Blindness and vision loss	0 (0.0)	1 (25.0)	0 (0.0)	1 (20.0)
Epilepsy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Guillain-Barré syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hearing loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heart failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infertility	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pelvic inflammatory disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other[6]	**N = 13**	**N = 23**	**N = 17**	**N=54 (6.7)**

	Global Burden of Disease
	Level I
	Level II
	Level III

[1] N=10 were multinational CRTs conducted in mixed economies, e.g., both low-income and lower-middle income countries.
[2] Level I, II, and III categories taken from the Institute for Health Metrics and Evaluation (IHME) Global Burden of Disease 2019 Cause and Risk Summary: https://www.healthdata.org/results/gbd_summaries/2019.
[3] Multiple selections are possible; frequencies do not add up to 100%.
[4] Other infectious diseases include: acute hepatitis; measles; and meningitis.
[5] Other non-communicable diseases include: congenital birth defects; endocrine, metabolic, blood, and immune disorders; gynaecological diseases; hemoglobinopathies and hemolytic anemias; oral disorders; sudden infant death syndrome; and urinary diseases.
[6] Other includes trials whose focus was: health education; health provider prescribing practices; health service or system improvements; general or overall child development; and general or unclassified health issue (e.g., delirium, fever, frailty, patients requiring antibiotics).