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Statistical analysis and handling of missing data in cluster randomized trials: protocol for a systematic review

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Statistical analysis and handling of missing data in cluster randomized trials: protocol for a systematic review

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ABSTRACT

Introduction: Cluster randomized trials (CRTs) randomize participants in groups, rather than individuals, and are key tools used to assess interventions in health research where treatment contamination is likely or if individual randomization is not feasible. Missing outcome data can reduce power in trials, including CRTs, and is a potential source of bias. The current review focuses on evaluating methods used in statistical analysis and handling of missing data with respect to the primary outcome in CRTs.

Methods and analysis: We will search for CRTs published between August 2013 and July 2014 using PubMed, Web of Science, and PsycINFO. We will identify relevant studies by screening titles and abstracts, and examining full text articles based on our pre-defined study inclusion criteria. 86 studies will be randomly chosen to be included in our review. Two independent reviewers will collect data from each study using a standardized, pre-piloted data extraction template. Our findings will be summarized and presented using descriptive statistics.

Discussion: This review will allow us to examine current statistical methods used in practice with respect to missing primary outcomes in CRTs. Based on our results, we will be able to make recommendations for areas where reporting and conduct may need improvement.

Ethics and dissemination: This methodological systematic review does not need ethical approval because there are no data used in our study that are linked to individual patient data. After completion of this systematic review, data will be immediately analyzed and findings will be disseminated through a peer-reviewed publication and conference presentation.

Keywords: Missing data; dropout; cluster randomized trials; bias

Strengths and limitations of this study

- To our knowledge, this is the first systematic review to evaluate statistical analysis and handling of missing outcome data in CRTs.
- Pre-specified search strategy, study selection criteria, and data extraction strategy, which minimizes the potential for bias during the review process.
- Study selection criteria encompass a wide range of CRTs including stepped wedge designs and feasibility studies.
- Pilot testing will be performed on several trials by three independent reviewers. Data collection will be carried out by two independent reviewers to ensure accuracy.
- Difficulty in identifying CRTs since many do not use the term 'cluster' in the title or abstract. To alleviate this issue, we will use other commonly used terms for cluster randomization including 'community randomized' or 'group randomized'.
- Subject to potential selection bias. Researchers who include terms such as 'cluster randomized' in the title or abstract may be more likely to follow the CONSORT statement compared to trials that do not include these terms. Researchers that do not realize their trials are CRTs are likely to use less robust methods.

INTRODUCTION

Cluster randomized trials (CRTs) randomize groups of participants to intervention arms, as opposed to individual participants. CRTs are frequently used in health research to minimize intervention arm contamination, or to assess interventions that can only be carried out at a cluster (e.g. physician, center) level.[1, 2]

Cluster level allocation generates several issues for statistical analysis. Participants cannot be assumed to be independent because of the similarity among participants within the same cluster. The intracluster correlation coefficient (ICC) is the statistical measure of this within-cluster dependence. Suppose some variable *y* was measured on *n* individuals divided into *k* clusters. The ICC, ρ, is the proportion of variance due to clustering, given by:

$$\rho = \frac{\sigma_k^2}{\sigma_k^2 + \sigma_e^2}$$

where σ_k^2 and σ_e^2 denote the between-cluster and within-cluster variances, respectively. Ignoring clusters in the analysis can lead to falsely low p-values, overly narrow confidence intervals, and increased type I error rates.[3, 4]

Missing data leads to a reduction of power, compromises the benefits of randomization, and is a potential source of bias. In practice, there will almost always be some missing data.[5, 6] Recent reviews in individual randomized trials have found that the majority has missing outcome data.[7-10] Missing data mechanisms have been broadly categorized into the following three

classes. Data are said to be missing completely at random (MCAR) if the reason for a missing observation is unrelated to observed values of the outcome and covariates. MCAR is a strong assumption and unlikely in most trials. A more reasonable assumption is missing at random (MAR), where missingness is independent of the pattern of missing values after conditioning on fully observed values. Lastly, data are considered missing not at random (MNAR) if missingness depends on the unseen value of that observation even after conditioning on fully observed data.[6, 11]

Several reviews have been published regarding CRTs.[12-22] Most have reported inadequate accounting for clustering in sample size and analysis. One review of CRTs published in 2011 focused on handling missing data, but did not discern between missing data in outcomes and covariates.[23] This distinction is necessary to determine the missing data assumption as well as appropriate methods for handling missing data. Thus, the primary aims of our review are to evaluate approaches used to analyze primary outcome data in CRTs and investigate methods used to handle missing outcome data in primary and sensitivity analysis. As a secondary aim, we will evaluate methods for achieving balance in CRTs by examining the proportions of CRTs that use stratification, matching, or minimization.

METHODS

Our systematic review will investigate statistical analyses and missing data strategies used in CRTs. This section contains an introduction of commonly used statistical approaches and missing data methods used for analyzing clustered data, followed by a detailed description of our methodological strategy.

Statistical Approaches for Analyzing CRTs

Two standard approaches to analyze CRTs include analysis at the cluster level and analysis at the individual level. Cluster level analysis involves reducing all observations within a cluster to a single summary measure, such as a cluster mean or proportion. Standard statistical tests (e.g. *t*-tests, linear regression models) can then be performed since each data point can now be considered independent.[4, 24] Even though cluster level analysis solves the problem of dependent data, reducing observations to single summary statistics leads to a reduction in sample size and as a result, statistical power. Modeling techniques incorporating individual-level covariates in cluster level analysis, such as generalized linear mixed models (GLMM) and generalized estimating equations (GEE), have also been developed.[25, 26] GEE and GLMM explicitly involve intracluster correlation in the modeling process, which enables a more realistic model of the clustered data. An advantage of these types of models is the ability to control for confounding at the individual level and reduce bias. However, drawbacks of this approach are that they are more computationally intensive and require a higher sample size of relatively large clusters.[24, 27]

Missing Data Methods in CRTs

Common approaches for handling missing outcome data include complete case analysis, single imputation, multiple imputation, and model based analysis. Complete case analysis excludes

participants with missing data and is only valid (produces unbiased estimates) under MCAR.[28] Single imputation strategies fill in missing data with a single value, thereby underestimating uncertainty. Under the MAR assumption, multiple imputation (MI) takes into account uncertainty by replacing each missing value with a set of possible values to create multiple imputed datasets. However, most implementations are single level, ignoring the hierarchical data structure of CRTs. In multilevel MI, the intracluster correlation can be represented if variability of imputed data reflects the multilevel structure of CRTs.[29] Model based methods include linear mixed models, valid for MAR data, if the model is specified correctly, and GEE which is valid under the stronger MCAR assumption as long as there are a large number of clusters.[27, 30]

Search Strategy

CRTs published in English between August 2013 and July 2014 will be sought. Two authors (MF, SH) will search for CRTs indexed in the following electronic bibliographic databases: PubMed, Web of Science (all databases), and PsycINFO. The search strategy will include the terms “cluster randomized [randomised]”, cluster and trial, “community trial”, “community randomized [randomised]”, or “group randomized [randomised]” found in titles and abstracts.

Inclusion and Exclusion Criteria

We will include all CRT designs, including stepped wedge trials.[31] We will exclude protocols of trials, observational studies, secondary reports of trials, studies in which no data were collected at the individual level and quasi-experimental cluster designs. Trials with survival outcomes will also be excluded, as missing time-to-event data are handled quite differently to other types of outcome data

Study Selection

Two independent reviewers (MF, SH) will identify eligible studies using the search strategy. All studies will be imported using EndNote (EndNote X6, Thomson Reuters, New York, USA). The reviewers will remove duplicates and go through titles and abstracts to identify eligible studies. Full text articles will be retrieved if the reviewer identified the article to answer ‘yes’ or ‘unclear’ to all selection criteria. The reviewers will collect and evaluate the full text article, and identify relevant studies based on study inclusion criteria. Reviewers will keep track of the number of studies excluded from each screening step.

Sample Size

We hypothesize 90% of trials having some missing outcome data. We estimate that a sample size of 86 papers will result in a margin of error of 6 percentage points (95% confidence interval of 84 to 96).

Data Extraction Strategy

Pilot testing of coding will be carried out with both reviewers (MF, SH) and the senior author (MB). All piloted papers will be included in the review. Two independent reviewers (MF, SH) will collect data from each study using a standardized, pre-piloted data extraction template. Disagreements over the eligibility or data extraction of particular studies will be handled by consensus or a third reviewer in the case that consensus was not achieved.

Extracted information will include: general information (journal, author, date of publication, pilot/feasibility study or stepped wedge), characteristics of the primary outcome (type of outcome, how often outcome was collected, how outcome was treated in the primary analysis), characteristics of study participants (unit or randomization, stratification/matching/minimization used, number of clusters randomized, total number of participants randomized, response rate at time period of primary analysis-if survey data), details of sample size calculation (accounted for clustering in calculation, reported ICC or coefficient of variation (CV), accounted for missing outcome data in calculation, reported attrition rate in sample size calculation), primary analysis (statistical method used in primary analysis, clustering accounted for in analysis, observed ICC or CV, GEE correction type), information on missing data (number (and proportion) of clusters with missing outcome, number (and proportion) of participants with missing outcome, method to handle missing data in primary analysis and sensitivity analysis). Specific details on data items, including relevant coding used during the data extraction process and definitions are given in Supplementary file 1.

Method of Analysis

We will present a synthesis of the findings by first describing characteristics of the primary outcome and study participants of the included studies.

We will then calculate the proportion of trials reporting some missing data at the individual and cluster level. Of those who reported some missing data, we will calculate the proportion of trials that carried out complete case analysis, simple imputation, multiple imputation, or model based methods (such as mixed models or GEE). Similar computations for trials that report sensitivity analysis for missing data will also be performed. We will quantify the number of trials who weakened the missingness assumption of their primary analysis to perform their sensitivity analysis as suggested by the Panel on Handling Missing Data in Clinical Trials, recently commissioned by the National Research Council.[6]

To evaluate prevention and planning, we will record whether sample size calculations were reported and if trials accounted for clustering and missing data. We will describe the details of analysis of primary outcomes and compare observed versus expected attrition rates and ICC's (or CV's).

DISCUSSION

To our knowledge, this is the first systematic review to evaluate statistical analysis and handling of missing outcome data in CRTs. We have a pre-specified search strategy, study selection criteria, and data extraction strategy. Systematic reviews are complicated and require judgments that should not rely on conclusions of the studies included in the review.[32] By pre-defining our methodology, we are minimizing the potential for bias during the review process. Additionally, our study selection criteria encompass a wide range of CRTs including stepped wedge designs and feasibility studies. Pilot testing will be performed on several trials by three

independent reviewers. Data collection will be carried out by two independent reviewers to ensure accuracy.

A limitation of this systematic review is the difficulty in identifying CRTs since many do not use the term 'cluster' in the title or abstract. In an effort to alleviate this issue, we will use other commonly used terms for cluster randomization including 'community randomized' or 'group randomized'. This allows us to reach a wider range of trials that may have been missed otherwise.

Furthermore, our systematic review is subject to potential selection bias. Researchers who include terms such as 'cluster randomized' in the title or abstract may be more likely to follow the CONSORT statement compared to trials that do not include these terms.[33] Researchers that do not realize their trials are CRTs are likely to use less robust methods.

Including studies with survival outcomes may influence missing data rates since participants are censored at dropout. We did not consider CRTs whose primary outcome was survival because different statistical issues arise in comparison to trials with non-survival outcomes.

This review will allow us to examine current statistical methods used in practice with respect to missing outcomes in CRTs. Based on our results, we will be able to make recommendations for areas where reporting and conduct may need improvement.

List of Abbreviations

CV	Coefficient of Variation
GEE	Generalized Estimating Equation
GLMM	Generalized Linear Mixed Model
ICC	Intracluster Correlation Coefficient
MAR	Missing at Random
MCAR	Missing Completely at Random
MI	Multiple Imputation
MNAR	Missing Not At Random

Authors' contributions:

MF and MB conceptualized the study. MF drafted the manuscript and incorporated comments from authors for successive drafts. SH and MB contributed to design and content. All authors read and approved the final manuscript.

Competing interests:

The authors declare that they have no competing interests.

Role of Funding Source:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Review Stage:

Data extraction

Data sharing statement:

After completion of this systematic review, data will be immediately analyzed and findings will be disseminated through a peer-reviewed publication and conference presentations.

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Supplementary file 1

Specific details on data items, including relevant coding used during the data extraction process.

Data items*

1. Year
2. Month
3. Journal
4. Author
    a. Last name of first author
5. Stepped wedge
    a. Yes, No
6. Pilot/feasibility
    a. Yes, No
7. If pilot/feasibility, were hypothesis tests performed?
    a. Yes, No, NA
8. If pilot/feasibility, were feasibility outcomes stated?
    a. Yes, No, NA
9. Outcome
10. Type of outcome
    a. Binary, Continuous, Count
11. How often outcome was collected at individual level
    a. Single, Repeated
12. How outcome was treated in the primary analysis
    a. Single, Repeated
13. Unit of randomization
    a. E.g. clinic, practitioner
14. Stratification/Matching/Minimization in randomization
    a. Stratification, Matching, Minimization, No
15. No. clusters randomized
16. No. clusters missing outcome
17. % missing - cluster level
18. Total no. participants randomized
19. No. participants missing outcome
20. % missing - individual level
21. If survey data, response rate at time period of primary analysis
22. Average no. participants per cluster
23. Min no. participants in cluster
24. Max no. participants in cluster
25. Presented sample size calculation
    a. Yes, No
26. Accounted for clustering in sample size
    a. Yes, No
27. Reported ICC or CV in sample size

28. Accounted for missing outcome data in calculation
    a. Yes, No
29. If yes, accounted missingness clusters and/or individuals
    a. Clusters, Individuals, Both, Unclear
30. Reported attrition rate in sample size
31. Primary analysis
32. Clustering accounted for in analysis
    a. Yes, No
33. Observed ICC or CV reported (primary outcome)
34. If so, how does it compare to ICC or CV used in sample size calculation?
    a. 100 * (Observed ICC – Sample size ICC) / Sample size ICC
35. GEE correction
    a. Yes, No, NA
36. If yes, what type?
    a. Bias correction, DF adjustment, Bootstrap
37. Method missing data in primary analysis
    a. Complete case, single imputation (LOCF, worst case, etc.), multiple imputation, mixed model, GEE, GEE IPW, Bayesian, Unclear
38. If imputation, was it multilevel?
    a. Yes, No, NA, Unclear
39. Sensitivity analysis
    a. Complete case, single imputation (LOCF, worst case, etc.), multiple imputation, mixed model, GEE, GEE IPW, Bayesian, No, Unclear
40. Level of reporting sensitivity analysis
    a. Sentence, Paragraph, Tabulation, NA
41. Notes

* If any item is not applicable, not reported or unclear, indicate “NA”, “NR” or “Unclear”, respectively, in appropriate field.

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Cluster level allocation generates several issues for statistical analysis. Participants cannot be assumed to be independent because of the similarity among participants within the same cluster. The intracluster correlation coefficient (ICC) is the statistical measure of this within-cluster dependence. Suppose some variable *y* was measured on *n* individuals divided into *k* clusters. The ICC, ρ, is the proportion of variance due to clustering, given by:

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observed data. Lastly, data are considered missing not at random (MNAR) if missingness depends on the unseen value of that observation even after conditioning on fully observed data.[6, 11]

Several reviews have been published regarding CRTs.[12-22] Most have reported inadequate accounting for clustering in sample size and analysis. One review of CRTs published in 2011 focused on imputation techniques with respect to handling missing data and did not discern between missing covariates or outcomes.[23] Modeling approaches can differ based on whether outcomes or covariates are missing: if covariates are missing, multiple imputation or an unadjusted model can be used. If outcomes are missing, maximum likelihood estimation using mixed models, for example, can provide unbiased estimation in certain cases (see below). Additionally, there was no distinction of whether trials used a complete case analysis, generalized estimating equations, or mixed models with respect to handling missing data in the primary analysis. Distinguishing between these methods is important, as they may provide valid estimates under certain missing data assumptions. Our objective is to provide a comprehensive review of analytical approaches for handling missing outcome data in CRTs. The primary aims of our review are to evaluate approaches used to analyze primary outcome data in CRTs and investigate methods used to handle missing outcome data in primary and sensitivity analysis. As a secondary aim, we will evaluate methods for achieving balance in CRTs by examining the proportions of CRTs that use stratification, matching, or minimization.

METHODS

Our systematic review will investigate statistical analyses and missing data strategies used in CRTs. This section contains an introduction of commonly used statistical approaches and missing data methods used for analyzing clustered data, followed by a detailed description of our methodological strategy based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[24]

Statistical Approaches for Analyzing CRTs

Two standard approaches to analyze CRTs include analysis at the cluster level and analysis at the individual level. Cluster level analysis involves reducing all observations within a cluster to a single summary measure, such as a cluster mean or proportion. Standard statistical tests (e.g. *t*-tests, linear regression models) can then be performed since each data point can now be considered independent.[4, 25] Even though cluster level analysis solves the problem of dependent data, reducing observations to single summary statistics leads to a reduction in sample size and as a result, statistical power. Modeling techniques incorporating individual-level covariates in cluster level analysis, such as generalized linear mixed models (GLMM) and generalized estimating equations (GEE), have also been developed.[26, 27] GEE and GLMM explicitly involve intracluster correlation in the modeling process, which enables a more realistic model of the clustered data. An advantage of these types of models is the ability to control for confounding at the individual level and reduce bias. However, drawbacks of this approach are that they are more computationally intensive and require a higher sample size of relatively large clusters.[25, 28]

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CRTs published in English between August 2013 and July 2014 will be sought. Two authors (MF, SH) will systematically search for CRTs indexed in the following electronic bibliographic databases: PubMed, Web of Science (all databases), and PsycINFO. The search strategy will include the terms “cluster randomized [randomised]”, cluster and trial, “community trial”, “community randomized [randomised]”, or “group randomized [randomised]” found in titles and abstracts. An example of our search strategy including search terms is found in Supplementary file 1.

Inclusion and Exclusion Criteria

We will include all CRT designs, including stepped wedge trials.[33] We will exclude protocols of trials, observational studies, secondary reports of trials, studies in which no data were collected at the individual level and quasi-experimental cluster designs. Trials with survival outcomes will also be excluded, as missing time-to-event data are handled quite differently to other types of outcome data

Study Selection

Two independent reviewers (MF, SH) will identify eligible studies using the search strategy. All studies will be imported using EndNote (EndNote X6, Thomson Reuters, New York, USA). The reviewers will remove duplicates and go through titles and abstracts to identify eligible studies. Full text articles will be retrieved if the reviewer identified the article to answer ‘yes’ or ‘unclear’ to all selection criteria. The reviewers will collect and evaluate the full text article, and identify relevant studies based on study inclusion criteria. Reviewers will keep track of the number of studies excluded from each screening step.

Sample Size

We hypothesize 90% of trials having some missing outcome data. We estimate that a sample size of 86 papers will result in a margin of error of 6 percentage points (95% confidence interval of 84 to 96).

Data Extraction Strategy

Pilot testing of coding will be carried out with both reviewers (MF, SH) and the senior author (MB). All piloted papers will be included in the review. Two independent reviewers (MF, SH) will collect data from each study using a standardized, pre-piloted data extraction template. Disagreements over the eligibility or data extraction of particular studies will be handled by consensus or a third reviewer in the case that consensus was not achieved.

Extracted information will include: general information (journal, author, date of publication, pilot/feasibility study or stepped wedge), characteristics of the primary outcome (type of outcome, how often outcome was collected, how outcome was treated in the primary analysis), characteristics of study participants (unit or randomization, stratification/matching/minimization used, number of clusters randomized, total number of participants randomized, response rate at time period of primary analysis-if survey data), details of sample size calculation (accounted for clustering in calculation, reported ICC or coefficient of variation (CV), accounted for missing outcome data in calculation, reported attrition rate in sample size calculation), primary analysis (statistical method used in primary analysis, clustering accounted for in analysis, observed ICC or CV, GEE correction type), information on missing data (number (and proportion) of clusters with missing outcome, number (and proportion) of participants with missing outcome, method to handle missing data in primary analysis and sensitivity analysis). If any of the items were unclear, including the amount of missing data and method used to handle missing data, we specified it as “unclear.” Specific details on data items, including relevant coding used during the data extraction process and definitions are given in Supplementary file 2.

Method of Analysis

Our analysis strategy follows closely after reviews by Wood et al.[7] and Bell et al.[10], which both assessed missing outcomes in individually randomized trials. We will present a synthesis of the findings by first describing characteristics of the primary outcome and study participants of the included studies. We will then calculate the proportion of trials reporting some missing data at the individual and cluster level. This will be determined from flow diagrams or text with respect to follow-up of clusters and individuals. Of those who reported some missing data, we will calculate the proportion of trials that carried out complete case analysis, single imputation, multiple imputation, GEE, or a mixed model to handle missing data in the primary analysis. Similar computations for trials that report sensitivity analysis for missing data will also be performed. We will quantify the number of trials who weakened the missingness assumption of their primary analysis to perform their sensitivity analysis as suggested by the Panel on Handling Missing Data in Clinical Trials, recently commissioned by the National Research Council.[6]

To evaluate prevention and planning, we will record whether sample size calculations were reported and if trials accounted for clustering and missing data. We will describe the details of analysis of primary outcomes and compare observed versus expected attrition rates and ICC’s (or CV’s). Quality of trials will not be assessed.

DISCUSSION

To our knowledge, this is the first systematic review to evaluate statistical analysis and handling of missing outcome data in CRTs. We have a pre-specified search strategy, study selection criteria, and data extraction strategy. Systematic reviews are complicated and require judgments that should not rely on conclusions of the studies included in the review.[34] By pre-defining our methodology, we are minimizing the potential for bias during the review process. Additionally, our study selection criteria encompass a wide range of CRTs including stepped wedge designs and feasibility studies. Pilot testing will be performed on several trials by three independent reviewers. Data collection will be carried out by two independent reviewers to ensure accuracy.

A limitation of this systematic review is the difficulty in identifying CRTs since many do not use the term 'cluster' in the title or abstract. In an effort to alleviate this issue, we will use other commonly used terms for cluster randomization including 'community randomized' or 'group randomized'. This allows us to reach a wider range of trials that may have been missed otherwise.

Furthermore, our systematic review is subject to potential selection bias. Researchers who include terms such as 'cluster randomized' in the title or abstract may be more likely to follow the CONSORT statement compared to trials that do not include these terms.[35] Researchers that do not realize their trials are CRTs are likely to use less robust methods.

Language bias may be introduced since we have limited our search to CRTs published in the English language.

Including studies with survival outcomes may influence missing data rates since participants are censored at dropout. We did not consider CRTs whose primary outcome was survival because different statistical issues arise in comparison to trials with non-survival outcomes.

This review will allow us to examine current statistical methods used in practice with respect to missing outcomes in CRTs. Based on our results, we will be able to make recommendations for areas where reporting and conduct may need improvement.

List of Abbreviations

CV	Coefficient of Variation
GEE	Generalized Estimating Equation
GLMM	Generalized Linear Mixed Model
ICC	Intracluster Correlation Coefficient
MAR	Missing at Random
MCAR	Missing Completely at Random
MI	Multiple Imputation
MNAR	Missing Not At Random

Authors' contributions:

MF and MB conceptualized the study. MF drafted the manuscript and incorporated comments from authors for successive drafts. SH and MB contributed to design and content. All authors read and approved the final manuscript.

Competing interests:

The authors declare that they have no competing interests.

Role of Funding Source:

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Review Stage:

Data extraction

Data sharing statement:

After completion of this systematic review, data will be immediately analyzed and findings will be disseminated through a peer-reviewed publication and conference presentations.

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Supplementary file 2
Specific details on data items, including relevant coding used during the data extraction process.

Data items*

1. Year
2. Month
3. Journal
4. Author
    a. Last name of first author
5. Stepped wedge
    a. Yes, No
6. Pilot/feasibility
    a. Yes, No
7. If pilot/feasibility, were hypothesis tests performed?
    a. Yes, No, NA
8. If pilot/feasibility, were feasibility outcomes stated?
    a. Yes, No, NA
9. Outcome
10. Type of outcome
    a. Binary, Continuous, Count
11. How often outcome was collected at individual level
    a. Single, Repeated
12. How outcome was treated in the primary analysis
    a. Single, Repeated
13. Unit of randomization
    a. E.g. clinic, practitioner
14. Stratification/Matching/Minimization in randomization
    a. Stratification, Matching, Minimization, No
15. No. clusters randomized
16. No. clusters missing outcome
17. % missing - cluster level
18. Total no. participants randomized
19. No. participants missing outcome
20. % missing - individual level
21. If survey data, response rate at time period of primary analysis
22. Average no. participants per cluster
23. Min no. participants in cluster
24. Max no. participants in cluster
25. Presented sample size calculation
    a. Yes, No
26. Accounted for clustering in sample size
    a. Yes, No
27. Reported ICC or CV in sample size

28. Accounted for missing outcome data in calculation
    a. Yes, No
29. If yes, accounted missingness clusters and/or individuals
    a. Clusters, Individuals, Both, Unclear
30. Reported attrition rate in sample size
31. Primary analysis
32. Clustering accounted for in analysis
    a. Yes, No
33. Observed ICC or CV reported (primary outcome)
34. If so, how does it compare to ICC or CV used in sample size calculation?
    a. 100 * (Observed ICC – Sample size ICC) / Sample size ICC
35. GEE correction
    a. Yes, No, NA
36. If yes, what type?
    a. Bias correction, DF adjustment, Bootstrap
37. Method missing data in primary analysis
    a. Complete case, single imputation (LOCF, worst case, etc.), multiple imputation, mixed model, GEE, GEE IPW, Bayesian, Unclear
38. If imputation, was it multilevel?
    a. Yes, No, NA, Unclear
39. Sensitivity analysis
    a. Complete case, single imputation (LOCF, worst case, etc.), multiple imputation, mixed model, GEE, GEE IPW, Bayesian, No, Unclear
40. Level of reporting sensitivity analysis
    a. Sentence, Paragraph, Tabulation, NA
41. Notes

* If any item is not applicable, not reported or unclear, indicate “NA”, “NR” or “Unclear”, respectively, in appropriate field.

Supplementary file 1

Search terms and strategy used in PubMed. The same search was also performed in Web of Science (all databases) and PsycINFO.

Cluster randomized OR cluster randomised OR community trial OR community randomized OR community randomised OR group randomized OR group randomised OR (cluster AND trial) Limiters: all in title or abstract, August 1, 2013 – July 31, 2014 1285 articles found

PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
REGISTRATION			
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	NA
AUTHORS			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
AMENDMENTS			
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
SUPPORT			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	NA
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	NA
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	4

Section/topic	#	Checklist item	Reported on page #
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
STUDY RECORDS			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4-5
DATA ITEMS			
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	5
OUTCOMES AND PRIORITIZATION			
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
RISK OF BIAS IN INDIVIDUAL STUDIES			
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
DATA SYNTHESIS			
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	5
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
META-BIAS(ES)			
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	NA
CONFIDENCE IN CUMULATIVE EVIDENCE			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	NA

BMJ Open

Statistical analysis and handling of missing data in cluster randomized trials: protocol for a systematic review

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Secondary Subject Heading:	Public health
Keywords:	Missing data, Dropout, Cluster randomized trials, Bias

Statistical analysis and handling of missing data in cluster randomized trials: protocol for a systematic review

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Word count: 2104

ABSTRACT

Introduction: Cluster randomized trials (CRTs) randomize participants in groups, rather than individuals, and are key tools used to assess interventions in health research where treatment contamination is likely or if individual randomization is not feasible. Missing outcome data can reduce power in trials, including CRTs, and is a potential source of bias. The current review focuses on evaluating methods used in statistical analysis and handling of missing data with respect to the primary outcome in CRTs.

Methods and analysis: We will search for CRTs published between August 2013 and July 2014 using PubMed, Web of Science, and PsycINFO. We will identify relevant studies by screening titles and abstracts, and examining full text articles based on our pre-defined study inclusion criteria. 86 studies will be randomly chosen to be included in our review. Two independent reviewers will collect data from each study using a standardized, pre-piloted data extraction template. Our findings will be summarized and presented using descriptive statistics.

Ethics and dissemination: This methodological systematic review does not need ethical approval because there are no data used in our study that are linked to individual patient data. After completion of this systematic review, data will be immediately analyzed and findings will be disseminated through a peer-reviewed publication and conference presentation.

Keywords: Missing data; dropout; cluster randomized trials; bias

Strengths and limitations of this study

- To our knowledge, this is the first systematic review to evaluate statistical analysis and handling of missing outcome data in CRTs.
- Pre-specified search strategy, study selection criteria, and data extraction strategy, which minimizes the potential for bias during the review process.
- Study selection criteria encompass a wide range of CRTs including stepped wedge designs and feasibility studies.
- Pilot testing will be performed on several trials by three independent reviewers. Data collection will be carried out by two independent reviewers to ensure accuracy.
- Difficulty in identifying CRTs since many do not use the term 'cluster' in the title or abstract. To alleviate this issue, we will use other commonly used terms for cluster randomization including 'community randomized' or 'group randomized'.
- Subject to potential selection bias. Researchers who include terms such as 'cluster randomized' in the title or abstract may be more likely to follow the CONSORT statement compared to trials that do not include these terms. Researchers that do not realize their trials are CRTs are likely to use less robust methods.

INTRODUCTION

Cluster randomized trials (CRTs) randomize groups of participants to intervention arms, as opposed to individual participants. CRTs are frequently used in health research to minimize intervention arm contamination, or to assess interventions that can only be carried out at a cluster (e.g. physician, center) level.[1, 2]

Cluster level allocation generates several issues for statistical analysis. Participants cannot be assumed to be independent because of the similarity among participants within the same cluster. The intracluster correlation coefficient (ICC) is the statistical measure of this within-cluster dependence. Suppose some variable *y* was measured on *n* individuals divided into *k* clusters. The ICC, ρ, is the proportion of variance due to clustering, given by:

$$\rho = \frac{\sigma_k^2}{\sigma_k^2 + \sigma_e^2}$$

where σ_k^2 and σ_e^2 denote the between-cluster and within-cluster variances, respectively. Ignoring clusters in the analysis can lead to falsely low p-values, overly narrow confidence intervals, and increased type I error rates.[3, 4]

Missing data leads to a reduction of power, compromises the benefits of randomization, and is a potential source of bias. In practice, there will almost always be some missing data.[5, 6] Recent reviews in individual randomized trials have found that the majority has missing outcome data.[7-10] Missing data mechanisms have been broadly categorized into the following three classes. Data are said to be missing completely at random (MCAR) if the reason for a missing observation is unrelated to observed values of the outcome and covariates. MCAR is a strong assumption and unlikely in most trials. A more reasonable assumption is missing at random (MAR), where missingness does not depend on the unobserved data, conditional on the

observed data. Lastly, data are considered missing not at random (MNAR) if missingness depends on the unseen value of that observation even after conditioning on fully observed data.[6, 11]

Several reviews have been published regarding CRTs.[12-22] Most have reported inadequate accounting for clustering in sample size and analysis. One review of CRTs published in 2011 focused on imputation techniques with respect to handling missing data and did not discern between missing covariates or outcomes.[23] Modeling approaches can differ based on whether outcomes or covariates are missing: if covariates are missing, multiple imputation or an unadjusted model can be used. If outcomes are missing, maximum likelihood estimation using mixed models, for example, can provide unbiased estimation in certain cases (see below). Additionally, there was no distinction of whether trials used a complete case analysis, generalized estimating equations, or mixed models with respect to handling missing data in the primary analysis. Distinguishing between these methods is important, as they may provide valid estimates under certain missing data assumptions. Our objective is to provide a comprehensive review of analytical approaches for handling missing outcome data in CRTs. The primary aims of our review are to evaluate approaches used to analyze primary outcome data in CRTs and investigate methods used to handle missing outcome data in primary and sensitivity analysis. As a secondary aim, we will evaluate methods for achieving balance in CRTs by examining the proportions of CRTs that use stratification, matching, or minimization.

METHODS

Our systematic review will investigate statistical analyses and missing data strategies used in CRTs. This section contains an introduction of commonly used statistical approaches and missing data methods used for analyzing clustered data, followed by a detailed description of our methodological strategy based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[24]

Statistical Approaches for Analyzing CRTs

Two standard approaches to analyze CRTs include analysis at the cluster level and analysis at the individual level. Cluster level analysis involves reducing all observations within a cluster to a single summary measure, such as a cluster mean or proportion. Standard statistical tests (e.g. *t*-tests, linear regression models) can then be performed since each data point can now be considered independent.[4, 25] Even though cluster level analysis solves the problem of dependent data, reducing observations to single summary statistics leads to a reduction in sample size and as a result, statistical power. Modeling techniques incorporating individual-level covariates in cluster level analysis, such as generalized linear mixed models (GLMM) and generalized estimating equations (GEE), have also been developed.[26, 27] GEE and GLMM explicitly involve intracluster correlation in the modeling process, which enables a more realistic model of the clustered data. An advantage of these types of models is the ability to control for confounding at the individual level and reduce bias. However, drawbacks of this approach are that they are more computationally intensive and require a higher sample size of relatively large clusters.[25, 28]

Missing Data Methods in CRTs

Common approaches for handling missing outcome data include complete case analysis, single imputation, multiple imputation, and model based analysis. Complete case analysis excludes participants with missing data and is valid (produces unbiased estimates) if missingness is independent of the outcome given covariates.[29] Single imputation strategies fill in missing data with a single value, thereby underestimating uncertainty. Under the MAR assumption, multiple imputation (MI) takes into account uncertainty by replacing each missing value with a set of possible values to create multiple imputed datasets. However, most implementations are single level, ignoring the hierarchical data structure of CRTs. Multilevel MI reflects the lack of independence found within clusters due to the multilevel structure of CRTs.[31, 32] Model based methods include linear mixed models, valid for MAR data, if the model is specified correctly, and GEE which is valid under the stronger MCAR assumption as long as there are a large number of clusters.[28, 33] Inverse probability weighting (IPW) is used to make a valid complete case analysis under MAR by weighting complete cases with the inverse of their probability of having data observed.[34] The IPW approach is relatively simple to carry out when missing values have a monotone pattern and can be applied to GEE. However, there is possible instability when weights are extremely large, which can lead to biased estimates and high variance in small samples.[6]

Search Strategy

CRTs published in English between August 2013 and July 2014 will be sought. Two authors (MF, SH) will systematically search for CRTs indexed in the following electronic bibliographic databases: PubMed, Web of Science (all databases), and PsycINFO. The search strategy will include the terms “cluster randomized [randomised]”, cluster and trial, “community trial”, “community randomized [randomised]”, or “group randomized [randomised]” found in titles and abstracts. An example of our search strategy including search terms is found in Supplementary file 1.

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Extracted information will include: general information (journal, author, date of publication, pilot/feasibility study or stepped wedge), characteristics of the primary outcome (type of outcome, how often outcome was collected, how outcome was treated in the primary analysis), characteristics of study participants (unit or randomization, stratification/matching/minimization used, number of clusters randomized, total number of participants randomized, response rate at time period of primary analysis-if survey data), details of sample size calculation (accounted for clustering in calculation, reported ICC or coefficient of variation (CV), accounted for missing outcome data in calculation, reported attrition rate in sample size calculation), primary analysis (statistical method used in primary analysis, adjustment (unadjusted, adjusted for design variables such as stratification, adjusted beyond stratification variables), clustering accounted for in analysis, observed ICC or CV, GEE correction type), information on missing data (number (and proportion) of clusters with missing outcome, number (and proportion) of participants with missing outcome, reasons for missing data, method to handle missing data in primary analysis and sensitivity analysis). If any of the items were unclear, including the amount of missing data and method used to handle missing data, we specified it as “unclear.” Specific details on data items, including relevant coding used during the data extraction process and definitions are given in Supplementary file 2.

Method of Analysis

Our analysis strategy follows closely after reviews by Wood et al.[7] and Bell et al.[10], which both assessed missing outcomes in individually randomized trials. We will present a synthesis of the findings by first describing characteristics of the primary outcome and study participants of the included studies. We will then calculate the proportion of trials reporting some missing data at the individual and cluster level. This will be determined from flow diagrams or text with respect to follow-up of clusters and individuals. Of those who reported some missing data, we will calculate the proportion of trials that carried out complete case analysis, single imputation, multiple imputation, GEE, or a mixed model to handle missing data in the primary analysis. Similar computations for trials that report sensitivity analysis for missing data will also be performed. We will quantify the number of trials who weakened the missingness assumption of their primary analysis to perform their sensitivity analysis as suggested by the Panel on

Handling Missing Data in Clinical Trials, recently commissioned by the National Research Council.[6]

To evaluate prevention and planning, we will record whether sample size calculations were reported and if trials accounted for clustering and missing data. We will describe the details of analysis of primary outcomes and compare observed versus expected attrition rates and ICC's (or CV's). Quality of trials will not be assessed.

DISCUSSION

To our knowledge, this is the first systematic review to evaluate statistical analysis and handling of missing outcome data in CRTs. We have a pre-specified search strategy, study selection criteria, and data extraction strategy. Systematic reviews are complicated and require judgments that should not rely on conclusions of the studies included in the review.[36] By pre-defining our methodology, we are minimizing the potential for bias during the review process. Additionally, our study selection criteria encompass a wide range of CRTs including stepped wedge designs and feasibility studies. Pilot testing will be performed on several trials by three independent reviewers. Data collection will be carried out by two independent reviewers to ensure accuracy.

A limitation of this systematic review is the difficulty in identifying CRTs since many do not use the term 'cluster' in the title or abstract. In an effort to alleviate this issue, we will use other commonly used terms for cluster randomization including 'community randomized' or 'group randomized'. This allows us to reach a wider range of trials that may have been missed otherwise.

Furthermore, our systematic review is subject to potential selection bias. Researchers who include terms such as 'cluster randomized' in the title or abstract may be more likely to follow the CONSORT statement compared to trials that do not include these terms.[37] Researchers that do not realize their trials are CRTs are likely to use less robust methods.

Language bias may be introduced since we have limited our search to CRTs published in the English language.

Including studies with survival outcomes may influence missing data rates since participants are censored at dropout. We did not consider CRTs whose primary outcome was survival because different statistical issues arise in comparison to trials with non-survival outcomes.

This review will allow us to examine current statistical methods used in practice with respect to missing outcomes in CRTs. Based on our results, we will be able to make recommendations for areas where reporting and conduct may need improvement.

List of Abbreviations

CV	Coefficient of Variation
GEE	Generalized Estimating Equation
GLMM	Generalized Linear Mixed Model
ICC	Intracluster Correlation Coefficient
MAR	Missing at Random
MCAR	Missing Completely at Random
MI	Multiple Imputation
MNAR	Missing Not At Random

Authors' contributions:

MF and MB conceptualized the study. MF drafted the manuscript and incorporated comments from authors for successive drafts. SH and MB contributed to design and content. All authors read and approved the final manuscript.

Competing interests:

The authors declare that they have no competing interests.

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Review Stage:

Data extraction

Data sharing statement:

After completion of this systematic review, data will be immediately analyzed and findings will be disseminated through a peer-reviewed publication and conference presentations.

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Supplementary file 1

Search terms and strategy used in PubMed. The same search was also performed in Web of Science (all databases) and PsycINFO.

Cluster randomized OR cluster randomised OR community trial OR community randomized OR community randomised OR group randomized OR group randomised OR (cluster AND trial) Limiters: all in title or abstract, August 1, 2013 – July 31, 2014 1285 articles found

Supplementary file 2

Specific details on data items, including relevant coding used during the data extraction process.

Data items*

1. Year
2. Month
3. Journal
4. Author
    a. Last name of first author
5. Stepped wedge
    a. Yes, No
6. Pilot/feasibility
    a. Yes, No
7. If pilot/feasibility, were hypothesis tests performed?
    a. Yes, No, NA
8. If pilot/feasibility, were feasibility outcomes stated?
    a. Yes, No, NA
9. Outcome
10. Type of outcome
    a. Binary, Continuous, Count
11. How often outcome was collected at individual level
    a. Single, Repeated
12. How outcome was treated in the primary analysis
    a. Single, Repeated
13. Unit of randomization
    a. E.g. clinic, practitioner
14. Stratification/Matching/Minimization in randomization
    a. Stratification, Matching, Minimization, No
15. No. clusters randomized
16. No. clusters missing outcome
17. % missing - cluster level
18. Total no. participants randomized
19. No. participants missing outcome
20. % missing - individual level
21. If survey data, response rate at time period of primary analysis
22. Average no. participants per cluster
23. Min no. participants in cluster
24. Max no. participants in cluster
25. Presented sample size calculation
    a. Yes, No
26. Accounted for clustering in sample size
    a. Yes, No
27. Reported ICC or CV in sample size

28. Accounted for missing outcome data in calculation
    a. Yes, No
29. If yes, accounted missingness clusters and/or individuals
    a. Clusters, Individuals, Both, Unclear
30. Reported attrition rate in sample size
31. Primary analysis
32. Clustering accounted for in analysis
    a. Yes, No
33. Observed ICC or CV reported (primary outcome)
34. If so, how does it compare to ICC or CV used in sample size calculation?
    a. 100 * (Observed ICC – Sample size ICC) / Sample size ICC
35. GEE correction
    a. Yes, No, NA
36. If yes, what type?
    a. Bias correction, DF adjustment, Bootstrap
37. Method missing data in primary analysis
    a. Complete case, single imputation (LOCF, worst case, etc.), multiple imputation, mixed model, GEE, GEE IPW, Bayesian, Unclear
38. If imputation, was it multilevel?
    a. Yes, No, NA, Unclear
39. Sensitivity analysis
    a. Complete case, single imputation (LOCF, worst case, etc.), multiple imputation, mixed model, GEE, GEE IPW, Bayesian, No, Unclear
40. Level of reporting sensitivity analysis
    a. Sentence, Paragraph, Tabulation, NA
41. Notes

* If any item is not applicable, not reported or unclear, indicate “NA”, “NR” or “Unclear”, respectively, in appropriate field.

PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
REGISTRATION			
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number	NA
AUTHORS			
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	7
AMENDMENTS			
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	NA
SUPPORT			
Sources	5a	Indicate sources of financial or other support for the review	7
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	NA
METHODS			
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	NA
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	4

Section/topic	#	Checklist item	Reported on page #
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	4
STUDY RECORDS			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	4
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	4
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	4-5
DATA ITEMS			
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	5
OUTCOMES AND PRIORITIZATION			
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	5
RISK OF BIAS IN INDIVIDUAL STUDIES			
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	5
DATA SYNTHESIS			
Data Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	5
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	5
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	NA
META-BIAS(ES)			
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	NA
CONFIDENCE IN CUMULATIVE EVIDENCE			
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	NA