Mapping outcome reporting bias in published non-pharmacological randomized trials: a protocol for a cross-sectional study

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Disclosures

Lucas Helal is head of the BRIGHTER Meta-Research Group and of the Centre for Journalology.

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Gabriel Costa, Charles Lucena, Bárbara Okabaiasse Dafne Port and Tammy Hoffmann are members of the BRIGHTER Meta-Research Group

Data-Sharing Statement

We will follow the International Committee of International Journal Editors recommendations for Data-Sharing. Data, statistical code, and research materials will be publicly available at the time of publication without restriction.

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Dissemination

We intend to publish our data in a biomedical journal and previously as a pre-print in the www.MedRxiv.org or www.MetaRxiv.org.

Introduction

Waste in research is avoidable through many pathways, such as addressing a valued research question, accurate and complete reporting, registering a minimal set of information of an experiment and addressing pre-specified outcomes (1-5). Randomized controlled trials (RCTs) are used to test the effectiveness of interventions. A trial registration involves filling data fields with information about a clinical trial at or before the time of first patient enrollment, being done in a trial registry platform. In 2005, ICMJE (International Committee of Medical Journals and Editors) policy mandating prospective trial registration as a condition of publication in member journals went into effect and RCTs started to be more frequently registered (6, 7).

However, the adherence to pre-specified methods and registration requirements can still be suboptimal today (2) and outcomes are often inadequately reported and pre-specified in the registry (8). Also, there is the problem of no registration and inadequate registration, that is, registration that is not done prospectively (after enrollment), in a concurrently or retrospectively manner, that is, when the trial is already ongoing or after the trial is finished (7, 9), even although too much guidance is available for reporting, registering and compliance to the protocol (e.g., www.equator-network.org; www.clinicaltrials.gov). The requirement for registering outcomes at trial inception is designed to address the selective publication of outcomes. The outcomes are one example of information that must be contained in the registry (10).

An outcome is defined as a variable that is intended to be compared between randomized groups to assess the benefits or harms of an intervention, which is measured in specific time points (11). It is an event in a person, used to assess a treatment effect (12). In this sense, an outcome may be defined using all following elements: 1 - outcome domain, 2 - specific measurement (or measure), 3 - specific metric, 4 - method of aggregation, and 5 - time point (or time frame) (12). For example, a domain can be: depression; a specific measure: Beck Depression Inventory score; a specific assessment time point: 12-month post randomization; a specific metric: change from baseline or final value; and a method of aggregation: mean or proportion (13). It can be considered a partially defined outcome one that has a domain, a measure and a time point (9, 13, 14), i.e., a minimum number of items is needed to define an outcome required by international registry platforms (7).

US Department of Health and Human services instructs for all Applicable Clinical Trials (ACTs), specially the funded by NIH, to report the specific measure (or measurement) and time point for each outcome at registration, reflecting the current international standards. However, when only a specific measurement or domain is registered, post hoc choices of the specific metric or method of aggregation can hide multiple comparisons and the transparency of statistical analyses. These two additional elements may only be defined at the time results are due. Because of this, an outcome may be considered only fully specified when all 5 elements are present (10).

Given the five possible elements that constitute an outcome and a difference in criteria required by international standards (3 elements), it can be considered an

adequately reported outcome one that is partially defined (with a domain, measure and time point) or even fully specified (if all 5 possible elements are present) being defined in the registry in a retrospective manner (6, 8, 9, 11-16). In this example, “mean change from baseline of Beck Depression Inventory score 12-month post randomization”, stated in the primary outcome section in a registry (done prospectively – before the initiation of the clinical trial) in clinicaltrials.gov platform (or other platform) with a registry number (13), would be considered a fully specified outcome (10) and hence adequately reported (13).

Different methods give different results when assessing the frequency of outcomes partially defined in samples of published RCTs (6). Multiple outcome definitions and multiple methods of analysis create opportunities to select results and this can also compromise meta-analysis, because outcomes need to be standardized in the literature to be synthesized when appropriate (12, 15, 17). A single outcome with a same domain can be reported differently according to other elements, for example, method of aggregation or specific measure in clinical trials assessing similar questions (12). This can occur for example to reach statistical significance, with a similar objective that outcomes are cherry picked as in major discrepancies (inconsistencies) literature, for example, when an outcome is omitted or changed from primary to secondary, even if these can be considered stronger changes when compared to simply changing an element, for example, changing the method of aggregation or measure between the registry and the publication of the trial (8, 11, 14).

In this sense, inconsistencies can occur when an outcome is reported in the trial results publication differently than stated in the trial registry, and it is common that the outcome can be stated in one way in the registry and in other way in the study publication (7, 18). Selective outcome reporting, major discrepancies and its implications are well studied in the literature (2, 8, 11). In this sense, these occurrences can only be studied when the trial has a registry and is also published later (8). However, there is the problem of lower registration rates and higher frequency of selective outcome reporting of non-pharmacological RCTs against published pharmacological RCTs, and this has only been analyzed in few research contexts and almost anecdotally.

To our knowledge, the frequency of how common selective outcome reporting and trial registration occur in non-pharmacological interventions is still scarce. Problems in outcomes have been studied to this date considering non-pharmacological interventions in separate of each other (19-25), and also some studies that analyzed this in a more systematic way had other focuses rather than analyzing the reporting of outcomes specifically (13, 19, 26, 27). Non-pharmacological interventions may include exercise, physical therapy, diet, nutrition, manual therapy, psychotherapy, rehabilitation, complementary and alternative medicine (28-30) constituting approximately 40% of clinical trials in the literature, and the number of these interventions will continue to raise in the future (31). These interventions (some of them – but not all – classified as non-regulated interventions) suffer in general from less

regulation from the industry than pharmacological trials (13, 19, 30, 32) and there are arguments that registries sometimes may not be well suited for them (19). Few journals in behavioral sciences or psychology, nursing, nutrition and dietetics, rehabilitation, and surgery require prospective trial registration (13). ClinicalTrials.gov is likely to be most complete for drugs and devices that are sponsored by the industry (10).

This said, the objective of this protocol is to describe the rationale and methods of a study that aims to estimate the prevalence of different outcome reporting biases and to map outcomes in RCTs of non-pharmacological interventions, also analyzing the frequency of registration of non-pharmacological trials. This study will explore the extent of selective outcome reporting of primary outcomes and of trial registration frequency in a sample of RCTs of published non-pharmacological interventions. We will also analyse the completeness of description of primary outcomes in this sample.

Objectives and Outcomes

Objectives

To analyse the extent of prospective registration and selective outcome reporting of primary outcomes in a sample of trials of non-pharmacological interventions and the completeness of reporting of primary outcomes.

Primary outcome

Proportion of prospectively registered non-pharmacological trials with selective outcome reporting of the primary outcome (primary outcome with major discrepancies).

Secondary outcomes

- a) proportion of non-pharmacological trials registered.
- b) proportion of prospectively registered non-pharmacological trials (from the total sample of registered non-pharmacological trials)
- c) proportion of non-pharmacological trials registered after enrolment (from the total sample of registered non-pharmacological trials)
- d) description of the completeness of outcomes of published non-pharmacological trials (from the total sample of prospectively registered non-pharmacological trials) with fully specified primary outcomes.

Design and Methodology

Inclusion and exclusion criteria

In this cross-sectional study, a sample of phase III/efficacy RCTs of non-pharmacological trials in humans published between July 1, 2019 to December 31, 2019 (6 months) will be collected, in MEDLINE/PubMed. RCTs will be eligible if the active/experimental interventions are non-pharmacological (excluding surgery, procedures and medical devices) (31).

We will search trial registries for each RCT. If the registry is not stated in the publication, ClinicalTrials.gov will be searched; the International Standard Randomized Controlled Trials Number registry (<http://www.isrctn.com>); and registries, if available, from the first and corresponding authors' countries. This search will be aided by the WHO registry search portal. For this search, we will use corresponding, first, and last author names and key terms. We will attempt to match the principal investigator, funding source, intervention, control group, and trial design of the RCT with registration records. If a registry entry cannot be found or ambiguity exists about the match, the corresponding author will be contacted once by email. If after this a registry cannot be found, the trial will be classified as not registered, and this will be quantified in the study (% of articles not registered) (9, 13). For each registered trial, we will classify it as registered prospectively, registered after enrollment or if the registration is unclear, according to Table 1 below.

Table 1. Classification of registration timing.

Registration - Definitions	
Registration date – registration timing	For each registered trial, we will classify the dates reported as being the registration date and the start and end dates of participant enrolment, and these will be used to determine whether registered randomized trials are registered prospectively, concurrently, or retrospectively. We will consider the registry stated in the publication of the trial.
Prospective registration	Is defined as registration of the trial before at or before the enrollment of the first patient in a given trial.
Registered after enrollment (after enrollment and retrospective registration)	Occurs after data collection is complete or after the beginning of enrollment.
Unclear registration	When the time of registration is unclear for some reason.

Table 1 – Timing of registration (7).

Trials in which participants are health professionals or students will be excluded. Ancillary analyses, interim analysis, follow-up papers, feasibility, phase 1 and subgroup analyses (secondary analysis) of previously reported RCTs will be also excluded. For

this, we will consider only the first publication. In cases of ancillary analysis or subgroup analysis, the registry of the main trial or the registry of the main trial plus ancillary analysis (NCTXXXXXXX-S000Y) will be considered. If there was no mention in the main registry of the outcome measured in subgroup/spinoff or registry for ancillary analysis for these specific cases, it will be classified as not registered. In cases of ancillary analysis, spin offs or subgroup analysis, if these were previously stated in registry, the registry of the main trial (primary registry) or the registry of the main trial with ancillary analysis (NCTXXXXXXX-S000Y) will be considered for assessing inconsistencies of outcomes. In this sense, if a subgroup analysis is realized post hoc being not previously adequately registered in the main trial, this will be characterized as inconsistent, if not clearly anticipated and determined as post-hoc.

Trials with nested economic evaluation (e.g., cost-effectiveness, cost-utility, cost-benefit etc.) will be excluded. We will not impose restrictions for trial in respect to hypothesis direction (i.e., superiority, non-inferiority or equivalence) or design (i.e., parallel, factorial, cluster, cross-over, etc.). Studies with multiple primary outcomes (>1 primary outcome) will be excluded. We will limit eligibility to trials published in English, Spanish or Portuguese. We will exclude trials whenever a pharmacological/device intervention is present.

We will exclude commentary or discussion articles, observational studies (cohort studies, case-control studies, and cross-sectional studies), meta-analyses, ongoing studies, articles for which only the abstract was available, follow-up studies, and duplicate publications. After reading the full-text article, studies with no primary outcome explicitly identified anywhere in the text and with no registry will also be excluded for analysis.

Study selection

A search strategy string (see Appendix 1) will be run in MEDLINE/PubMed and we will report it here accordingly to the PRISMA-S (33). Our search strategy will comprise only two databases (MEDLINE/PubMed) without tables of contents, conferences, proceedings, etc., for reasons of feasibility. The references will be retrieved only in the indexed databases. Snowballing by contacting authors will not be necessary accordingly to our piloted search strategy. The query will be run directly at the database without Ovid. We will not limit the search strategy for language, but we will limit it for randomized clinical trials published between July 1, 2019 to December 31, 2019 (6 months). The highly sensitive filter for RCTs will be used (34). All retrieved reports will be checked for eligibility by four assessors independently. Reviewers will screen titles and abstracts only, and full text will be checked for those articles that remain after screening to confirm RCT status and that it was a non-pharmacological intervention evaluated. We will use EndNote X9 software for managing data during the selection process. We will select eligible articles (non-pharmacological interventions) manually in EndNote after performing the search strategy for RCTs (34) in the time frame proposed in ([Inclusion and Exclusion Criteria](#)). The list of included and excluded studies

will be made available at the finalization of the search strategy. The full search strategy is presented in the Appendix 1.

Data extraction

The data extraction process will be also conducted by two assessors independently, with disagreements resolved through consensus or by consulting a third author when necessary. Extractors will use a pilot-tested spreadsheet developed for the study, where reviewers will enter the variables of interest.

Defining a primary outcome

Table 2. Criteria for characterization of the outcomes.

Outcome - Definitions	
Outcome	An outcome is defined as a variable that was used to compare randomized groups to assess the efficacy or harm of the intervention.
Primary Outcome	Explicitly described as “primary,” “key,” or “main” outcomes (or endpoints) in the relevant document. If none is explicitly specified, then it will be considered as primary outcome the one used for power calculation (in the case when analyzing publication, since the registry will not mention power calculation).
Nonprimary Outcome	The outcomes (or endpoints) that are explicitly define as “secondary” or the ones that are not explicitly defined as primary. If no primary outcome is specified for a trial and there was no power calculation, all outcomes will be considered nonprimary.
Partially Defined Outcome	An outcome that has a domain, measurement (or measure) or specific metric and time-point (or time frame), reflecting international standards (10).
Fully Specified Outcome	An outcome that has all five elements, i.e., domain, measurement (or measure), metric, time-point (or time frame) and method of aggregation (10). For example: mean change from baseline of Beck Depression Inventory total score 12-month post randomization.
Adequately Reported Outcome	An outcome that is partially defined or fully specified and correctly pre-specified, that is, stated in the registry in a prospective manner (prospective registration – that is, any trial that is registered being this registration not done after the first patient is enrolled).

Table 2 – Characterizing outcomes as primary and nonprimary.

Only outcomes adequately reported (see Table 2) will be analyzed for selective outcome reporting. We will classify a primary outcome as selective reported if: 1 - the registered primary outcome is reported as a nonprimary outcome in the published report, 2 - the registered primary outcome is omitted in the published report, 3 - a new primary outcome is introduced in the published report (i.e., a registered nonprimary outcome becomes a primary outcome in the published report or an outcome that did not appear at all in the registry entry is introduced as a primary outcome in the published report), 4 - the published primary outcome is described as a nonprimary outcome in the registry entry (i.e., a subset of category 3), 5 - the timing of assessment of the registered and published primary outcomes differs, 6 – the measure of the registered and published primary outcomes differs, 7 – the metric (when present) of the registered and published primary outcomes differs and 8 – when the method of aggregation (when present) of the registered and published primary outcomes differs. When none of these 8 discrepancies are present, the primary outcome will be defined as consistent. We are starting from a criteria defined by Chan et al. (8, 14) and extending it to embrace the metric, measure and the method of aggregation, apart from domain and time point (these two embraced in Chan's criteria), between the registry and the publication. Examples are provided below in Table 3.

Table 3. Examples of selective outcome reporting when major discrepancies are present between the registry and the trial.

Inconsistencies	
Inconsistencies – Example	For example, a major discrepancy between the registered and published primary outcomes can be as follows: if the 2 are clearly different (e.g., blood pressure and death) or are evaluated at a different times (e.g., pain at 3 months and pain at 6 months) (14).
Inconsistencies – Other Examples	Other examples of major discrepancies can be found in the article of Chan et al. (2006). They are the following: <ul style="list-style-type: none"> o Outcome (e.g., percentage of patients with severe cerebral bleeding) changed from primary to secondary o Prespecified primary outcome (e.g., event-free survival rate) omitted from published reports o Outcome (e.g., overall symptom score) changed from secondary to primary o Outcome (e.g., percentage of patients with graft occlusion) listed as a new primary outcome (i.e., not mentioned in the protocol)

We will describe the outcomes of efficacy and classify them in a database. For each registered randomized trial, 2 investigators will independently examine the trial registry entry (including its history of amendments) and the published trial report and extract the information (variables of the study - variables section). Any disagreements between authors results will be adjudicated by a third individual not involved in including the studies. These variables will be collected and inserted in the excel spreadsheet of RCTs collected.

Since we will study the frequency of selective outcome reporting and for this we will analyze each primary and nonprimary outcome between the study registry and publication, we will conduct a second study in which we will analyze if the outcomes in

this sample of RCTs of non-pharmacological interventions are completely and adequately reported, according to a specific methodology described below.

Methodology for considering outcomes completely and adequately registered

Primary outcomes will be considered partially defined if it has the domain, measurement (or measure) or metric and time-point (or time frame) in the registry. If the outcome has all five elements including method of aggregation, it will be characterized as fully specified. We are going to classify trials as adequate registered if they were prospectively registered with partially defined primary and nonprimary outcomes. If not, we will rate the adequacy of registration as inadequate, together with reasons. In Table 2 of this protocol this is explained in table format.

For example, “lung function” is considered incomplete on both criteria. Specifically, a specific measurement of the primary outcome can be for example: Beck Depression Inventory score (not simply depression); a domain: depression; a specific assessment time point: 12-month post randomization; a specific metric: change from baseline, final value; and a method of aggregation: mean or proportion. For more examples of outcomes elements, see below in Table 4 and in Figure 1.

Table 4. Five elements of an outcome.

Outcome Elements - Explanation and definitions	
Outcome Elements – Example 1	“a specific measurement of the primary outcome or outcomes (eg, Beck Depression Inventory score, not simply depression), a specific assessment time point (eg, 12-month post randomization), a specific metric (eg, change from baseline, final value), and a specific method of aggregation (eg, mean, proportion)” (13).
Outcome Elements – Example 2	outcome domain, specific measure, specific metric, method of aggregation, and time point. For example, “proportion of participants with 50% change from baseline to 8 weeks on the MADRS total score (12).
Outcome Elements – Example 3	Domain – anxiety, specific measure or measurement - Hamilton Anxiety Rating Scale, specific metric – change from baseline, method of aggregation - mean change from baseline and specific time frame – 52 weeks (7).
Outcome Elements – Example 4	Domain – anxiety, specific measure or measurement - Hamilton Anxiety Rating Scale, specific metric – e.g., change from baseline at specified time, method of aggregation – e.g., categorical such as proportion of participants with a decrease greater than or equal to 50%.

For practical examples see Table S1 of Zarin et al. (7). More examples can also be found in another publication of Zarin et al (7).

These variables will be collected and inserted in the excel spreadsheet of RCTs previously collected. The data extraction process will be also conducted by two assessors independently, with disagreements resolved through consensus or by consulting a third author when necessary.

Statistical Analysis

Variables, primary and secondary outcomes will be described as absolute and relative frequencies. Descriptive variables will be presented as mean and standard deviation or median and interquartile range if continuous variables and, in the case of dichotomization/categorization, originally collected continuous variables will be transformed accordingly and will be presented as absolute and relative frequencies. No inferential analysis is planned a priori. However, due to the nature of this exploratory study, the team may decide to estimate associations between variables in an exploratory manner (without any intention of recommendation or decision-making) and an update version of the protocol will be uploaded (that being the case, settings for inferential analysis such as type 1 error threshold will be presented accordingly). Statistics and plots will be generated through the R software with the RStudio interface linked, version 3.5.3, for Mac and Windows.

Limitations of this protocol

At least for the time of the writing of this manuscript, we anticipate such limitations for the future study to be conducted, but not limited to recognize further limitations thereafter. Since our protocol proposes two cross-sectional studies analyzing outcomes trials already published in the literature, it will not have temporality and monitoring of outcomes, as is the case of studies that accompany the trials since first registry until publication, as for example COMpare (35) and others (11).

Variables

1) Trial registration (registered/not registered)

1.1) Is the trial registered with more than 1 registries? (yes/no)

1.1.1) number of registries

1.2) Date of trial registration

1.3) Date of trial publication

1.4) Is the trial registered

1.4.1) Prospectively - before or at the enrollment of the first patient

1.4.2) After enrollment registration – during or after the conduction of the trial

1.4.3) Unclear

1.5) Registration database (i.e., ClinicalTrials.gov, or others)

1.6) If prospectively registered, time lag between registration and publication of the RCT

2) Registered and published primary outcome

2.1) Completeness of registered primary outcome

2.1.1) Registered primary outcome domain

2.1.2) Registered primary outcome measurement (or measure)

2.1.3) Registered primary outcome metric

2.1.4) Registered primary outcome time point (or time frame)

2.1.4) Registered primary outcome method of aggregation

2.1.5) Primary outcome in registry partially defined? (yes/no)

2.1.6) Primary outcome in registry is fully specified? (yes/no)

2.2) Completeness of published primary outcome

2.2.1) Published primary outcome domain

2.2.2) Published primary outcome measurement (or measure)

2.2.3) Published primary outcome metric

2.2.4) Published primary outcome time point (or time frame)

2.2.4) Published primary outcome method of aggregation

2.2.5) Is the primary outcome partially specified in the publication?

2.2.6) Published primary outcome is fully specified? (yes/no)

Obs.: For multiple primary outcomes, variables in 2) will be collected for each one.

3) Inconsistencies between the registered and published primary outcomes

3.1) The registered primary outcome is reported as a nonprimary outcome in the published report (yes/no)

3.2) The registered primary outcome is omitted in the published report (yes/no)

3.3) A new primary outcome is introduced in the published report (yes/no)

3.4) The published primary outcome is described as a nonprimary outcome in the registry entry (yes/no)

- 3.5) The registered and published primary outcomes differ? (yes/no)
- 4) Other characteristics of the trial (as reported in the published trial report)
 - 4.1) Continent/region of first author (corresponding author)
 - 4.2) Country of first author
 - 4.3) Journal Impact Factor
 - 4.4) Type of NPT intervention (we will extract the name/phrase of the intervention, as reported in the trial, and categorize later due to the existent variety and difficulty to anticipatedly categorize).
 - 4.5) Type of funding source
 - 6.5.1) Industry
 - 6.5.2) Industry and non-industry
 - 6.5.3) Non industry
 - 6.5.4) Stated that there was no funding
 - 6.5.5) Not reported
 - 6.6) Sample size in publication
 - 6.7) Conflict of interest reported (yes/no/unclear)
 - 6.8) Number of outcomes measured (both primary and secondary)
 - 6.9) Presence of subgroup analysis (yes/no/unclear)
 - 6.10) Number of treatment groups
 - 6.11) Type of trial (crossover, parallel...)
 - 6.12) Hypothesis direction (i.e., superiority, non-inferiority, equivalence)
 - 6.13) Language of published trial

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