Trials

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Reporting of justifications for withholding established effective interventions in randomised placebo-controlled trials: a systematic review

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Abstract

Background Randomised-controlled-trials (RCTs) are crucial for assessing the efficacy of new treatments. Some RCTs are placebo-controlled, which is uncontroversial when there is no established effective intervention or when a placebo is added to one. However, withholding an established effective intervention from participants requires justification.

Aim and objectives This systematic review aims to examine reporting practices around withholding established effective interventions from participants in placebo-controlled RCTs. Our objectives are (i) to determine the frequency with which established effective interventions are withheld in placebo-controlled RCTs without reported justification; (ii) to ascertain whether these relate to control arms only or both; (iii) to ascertain whether research participants are communicated this information; and (iv) explore factors associated with this practice.

Methods Protocols of placebo-controlled RCTs, published in the journal *Trials* in 2022, were identified. Full-text of included protocols and available materials were accessed to estimate the proportion that withheld established effective interventions without reported justification. The withholding of effective interventions was categorised as either withholding a known effective intervention from the placebo arm or withholding a known effective concomitant treatment from both arms. We explored associations with: study conduct region, industry sponsorship, therapeutic area and complementary medicine.

Results A total of 134 protocols met the inclusion criteria. Only a minority (27, 20%) provided participant-facing material. Of these 134 protocols, (14, 10%) were identified as withholding effective interventions without reported justification. The majority (12, 86%) involved withholding concomitant medications in both arms, whilst (2,14%) withheld effective interventions from only the placebo arm; none reported justification in the participant-facing materials (although in only one was this material available). Most (9, 64%) of the protocols that withheld effective interventions, without reported justification, were conducted in Asia; most were testing complementary medicines (10, 71%); only (3, 21%) were industry-sponsored.

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Conclusion In this sample of protocols published in Trials in 2022, 10% withheld an established effective intervention without a reported justification, and this mostly related to withholding effective concomitant medications from both study arms. The majority of studies do not make their participant facing material available and so it cannot be determined what information is provided to study participants.

Keywords Randomised-controlled-trials (RCTs), Placebo, Concomitant medications, Ethics

Background

Randomised controlled trials (RCTs), essential tools in medical research, assess the effectiveness of an experimental intervention in a prospective manner. Provided they are conducted robustly, RCTs can eliminate much of the bias that is found in other non-randomised study designs [1]. But deciding on an appropriate control intervention can be ethically and methodologically challenging. While RCTs generally compare a novel intervention against a known effective or widely used intervention, some RCTs involve a placebo control. Placebo-controlled RCTs use an inert sham intervention designed to isolate the effects of the experimental intervention by blinding research participants to whether they receive the intervention under investigation or the control [2].

Whether it is ethically permissible to conduct a placebo-controlled RCT has been the focus of much debate in the research ethics literature [3]. The growing consensus is that the use of placebo is uncontroversial when there is no established effective intervention for the condition of interest, or when the placebo is used in addition to an established effective intervention in the control arm. However, withholding an established effective intervention from participants in either the control or active intervention arm requires justification.

According to the Council for International Organizations of Medical Sciences international ethics guidelines, the use of placebo as a comparator without providing an established effective intervention to participants is justified only if "withholding such interventions is methodologically necessary and exposes participants to no more than a minor increase above minimal risk" [4]. The onus falls on researchers to clearly explain in their study protocol that these conditions are met so research ethics committees can ensure that research participants will not be denied competent medical care and that their health and welfare are adequately protected. Indeed, in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines, item 6b requires researchers provide an explanation for the choice of control interventions [5]. Additionally, international and national ethics guidelines require researchers to disclose, at a minimum, information about the aims, methods and the anticipated benefits and potential risks of the study (including the use of placebo) to prospective participants during the informed consent process [6].

However, it remains unclear whether researchers report justifications for withholding established effective interventions from participants in placebo-controlled RCTs in either their study protocols or participant-facing materials. To examine reporting practices around withholding established effective interventions, we conducted a systematic review of study protocols for placebo-controlled RCTs published in the journal *Trials* in 2022. Our specific objectives are (i) to determine the frequency with which established effective interventions are withheld in placebo-controlled RCTs without reported justification; (ii) to ascertain whether these relate to control arms only or both arms; (iii) to ascertain whether research participants are communicated this information; and (iv) to explore factors associated with this practice.

Methods

This systematic review is reported according to the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-Analysis PRISMA checklist [7].

Search strategy

The journal *Trials* was searched to identify protocols of placebo-controlled RCTs, published in the calendar year 2022, accessed through Medline. For feasibility reasons, we only searched one calendar year (2022) choosing a recent year to reflect a contemporary sample. *Trials* was chosen as it is commonly used among researchers to publish their study protocols, authors are required to upload the SPIRIT checklist (which facilitates protocol navigation), and all protocols are reviewed by a protocol editor to ensure that they adhere to the SPIRIT guidelines.

Inclusion and exclusion criteria

We included full-text protocols of placebo-controlled RCTs published in *Trials* from 1 January 2022 to December 31, 2022, as well as all publicly available supplementary documents which were available under the additional files section in *Trials* (e.g. consent forms or other participant-facing material, SPIRIT checklists and ethics approval documents). All protocols published in *Trials* were available in English; any supplementary documents published in languages other than English were

translated using Google Translate. We excluded final study reports, pilot and feasibility studies, secondary analyses, statistical analysis plans and systematic reviews. To ensure a contemporary sample, we also excluded any updates to protocols published in other years. We also excluded protocols for placebo-controlled RCTs using a crossover design, as there may be a perception that there are different requirements with respect to withholding established effective interventions when all participants receive both experimental and control interventions.

Study selection

Titles and abstracts of retrieved protocols were screened for inclusion by a single reviewer (HA). Those assessed as potentially eligible during title and abstract screening underwent a full-text review for inclusion, carried out independently and in duplicate (AG and HA).

Data extraction: study characteristics

Data were extracted on study location, location of main funder, location of research ethics committee, study design (parallel arm or other), study purpose (efficacy, efficacy and safety, or other), study size (number randomized < 200 or > = 200), therapeutic area (non-communicable disease, communicable disease, Covid-19 and non-Covid-19), whether the intervention consisted of complementary or alternative medicine (e.g. acupuncture, herbal medicine), whether allocation concealment was reported, and whether the study was sponsored or funded by a commercial company. Data were also extracted on whether ethics approval was reported as granted and whether participant-facing information relating to the informed consent process (e.g. consent forms, participant information leaflets) was available. Data describing study characteristics was extracted by one reviewer (HA).

Justification for study characteristics collected

The study characteristics collected were chosen by considering general descriptive items (such as study design and sample size) and factors which were *a priori* thought to be potentially associated with the reporting of withholding established effective interventions. We chose to categorize study characteristics based on convenient cut-points; for example, as most studies used a parallel design, we simply report the proportion with a parallel design to avoid reporting numerous categories.

We explored associations with location of study conduct, industry-sponsorship, therapeutic area, and if it is complementary medicine. Location of the study, main funder and research ethics committee (each of which might differ in any given study) were considered because countries may have different ethics and regulatory frameworks, as well as cultural research norms and practices that might contribute to disparities in reporting practices [8]. Industry-sponsorship was chosen as a factor for consideration because trials funded by pharmaceutical companies can have financial gains from successful trial outcomes, which might influence the methodology such as the choice of comparator [9]. Therapeutic area was considered as a possible explanatory factor because different therapeutic areas, such as communicable and non-communicable diseases, face different challenges in identifying effective interventions and so may show more or less propensity for withholding established effective interventions [10, 11]. Moreover, conditions causing public health emergencies, including but not limited to Covid-19, might be considered as a context in which standard ethics requirements can be modified or overridden [12]. Finally, we explored associations with complementary or alternative medicine because, although their use is gaining popularity, concerns have arisen regarding their safety and quality of evidence of effectiveness [13].

Data extraction: outcomes

The identified protocols were classified according to whether the trial appeared to withhold established effective interventions from participants in the control arm, or concomitant medications from all participants, or both, without a clearly reported justification. A protocol was classified as withholding an established effective intervention without justification when all three of the following criteria were met: (i) the intervention was withheld from participants; (ii) the protocol authors cited evidence or explicitly stated that the intervention was effective for the condition under study; and (iii) no justification was reported for this withholding. A justification was considered reported if the protocol provided one or more reasons for the decision to withhold the intervention, for example, stating that withholding the intervention posed no more than minimal risk to participants. This classification was implemented using a checklist (Supplementary Material S1). The checklist identified if the authors claimed that a given intervention was effective (citing evidence to this effect) and then proceeded to state that this intervention was withheld (from either or both arms), without reporting any justification. We did not assess whether the citing evidence about the effectiveness of the intervention was of high quality.

This categorization of studies was conducted independently and in duplicate (AG and HA). Disagreements were resolved by discussion (HA, AG and KH). For every study identified as potentially withholding an established effective intervention without reporting a justification,

we extracted the relevant text relating to the citation of the evidence that the intervention is effective along with the relevant text from the protocol that identifies that this intervention was withheld from participants.

Methods of analysis

A descriptive summary of the included protocols is reported. We describe the included studies by reporting the numbers and percentages under each of the levels of the characteristics chosen to summarize the studies. We then describe the number and proportions for each of the key outcomes. To understand the underlying contextual factors contributing to such practices, we compare the frequency of outcomes with respect to each of the study characteristics collected, reporting odds ratios, 95% confidence intervals and *p*-values derived from exact t-distributions using Stata 17.

Results

Search results

The search was conducted on 14 May 2023 and identified 168 potential articles for inclusion. After title and abstract screening, 32 studies were excluded, and the remaining 136 protocols underwent a full-text review. An additional two articles were excluded, leaving 134 protocols meeting the eligibility criteria. The PRISMA flow diagram is presented in Fig. 1.

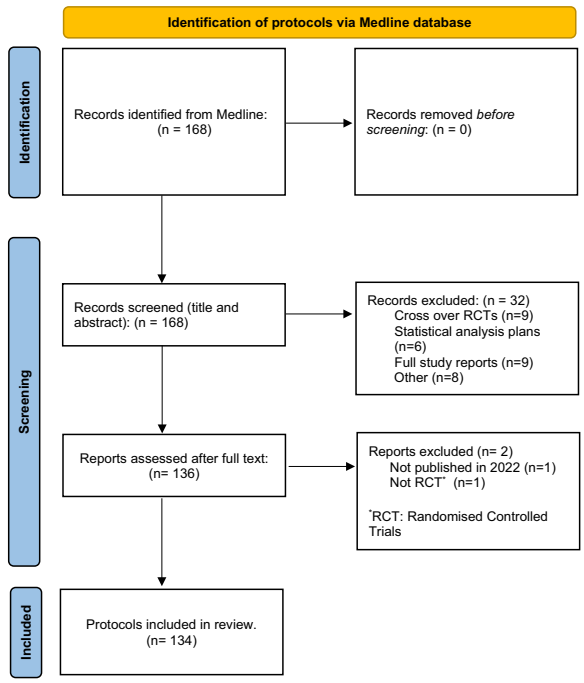


Fig. 1 PRISMA flow diagram

Table 1 Characteristics of included protocols

Characteristic	n = 134
Region of study conduct	
Europe	50 (37.3%)
Asia	50 (37.3%)
North America	14 (10.4%)
South America	7 (5%)
Australia and New Zealand	5 (4%)
Africa	8 (6%)
Ethical approval granted[1]	127 (95%)
Informed consent form availability	27 (20%)
Therapeutic area	
Non-Communicable disease	114 (85%)
Communicable disease	20 (15%)
Covid-19[2]	12 (9%)
Non-Covid-19	122 (91%)
Complementary medicine[3]	54 (40%)
RCT design	
Parallel arm	120 (90%)
Other[4]	14 (10%)
Purpose of RCT	
Efficacy	71 (53%)
Efficacy and Safety	46 (34%)
Other (Miscellaneous)[5]	17 (13%)
Allocation concealment reported	107 (80%)
Industry-sponsored[6]	16 (12%)
Trial size (< 200 participants)	89 (66%)
Region of first research ethics committee	
Europe	51 (38%)
Asia	50 (37.3%)
North America	14 (10.4%)
South America	7 (5.2%)
Australia and New Zealand	5 (4%)
Africa	7 (5.2%)
Region of funding	
Europe	53 (40%)
Asia	50 (37%)
North America	18 (13%)
South America	7 (5%)
Australia and New Zealand	5 (4%)
Africa	1 (1%)

[1] Some protocols were still awaiting ethical approval at the time of publication

[2] 71.EC_RCT_Gorman_May2022 [14] is partially Covid-19, therefore it was considered as Covid-19 and a communicable disease

[3] Complementary medicine: defined as a non-conventional therapy used alongside Western medicine (e.g., acupuncture, meditation, chiropractic care)

[4] Other: factorial, add-on, cluster and adaptive

[5] Other: includes safety, mechanism of action, dose-finding and other miscellaneous purposes

[6] Trials funded by pharmaceutical companies

Study characteristics

The characteristics of the 134 included protocols are detailed in Table 1. Many were conducted in Europe (50, 37%) or Asia (50, 37%). The majority (127, 95%) reported obtaining research ethics committee approval. Only 27 (20%) included any participant-facing material in their supplementary material. The majority investigated interventions for non-communicable diseases (114, 85%) as opposed to communicable disease (20, 15%); and among those 20 studies, 12 studies were related to COVID-19. Complementary medicine studies were common (54, 40%). Almost all used a parallel-arm design (120, 90%); and the most common study objective was testing efficacy (71, 53%). Of the 134 protocols, 107 (80%) reported allocation concealment; only 16 (12%) were industry sponsored; and the majority (89, 66%) had a total sample size of less than 200.

Findings with respect to potentially withholding established effective interventions

Among the 134 protocols, 14 (10%) protocols were classified as withholding established effective interventions without reported justification (Table 2). Of these, the majority (12, 86%) involved withholding concomitant medications, and two (14%) were classified as withholding established effective interventions from the placebo arm only. Among those 14 protocols, only 1 (7%) had participant-facing material available and this did not include a justification for withholding an established effective intervention (Supplementary Material S2). Setting, context and factors leading to withholding established effective interventions in the identified 14 protocols are reported in Supplementary Material S3.

Association between withholding effective interventions and contextual factors

Table 3 shows how contextual factors are associated with the protocols identified as withholding established effective interventions without reported justification. These protocols were more likely to have been conducted in Asia (64% vs 36%, $p=0.04$, Odds Ratio 3.47 (95% CI 0.96–13.93)) and more likely to test complementary medicines (71% vs 37%, p = 0.019, Odds Ratio 4.32 (95% CI 1.15–19.80)). There was no significant difference between industry-sponsored and non-industry sponsored (21% v 11%, p = 0.37, Odds Ratio 2.24 (95% CI 0.35–10.10)) and minimal differences between therapeutic areas.

Table 2 Quality of reporting of justification for withholding effective interventions

Occurrence of key outcomes	***n*** **= 134**
Withholding effective interventions (without reported justification)	14 (10%)
Withholding effective interventions categories	***n*** **= 14**
Withholding concomitant medications	12 (86%)
Withholding effective intervention from the placebo arm	2 (14%)
Information provided to participants in informed consent*	0 (0%)

* In only one study was informed consent material available

Table 3 Comparison between protocols with withholding effective interventions (without reporting justification) and those without in regard to contextual factors

	Withholding effective interventions without justification	
	Yes (*n* = 14)	**No (*n* = 120)**
Region of conduct		
Europe	1 (7.1%)	49 (41%)
Asia	9 (64.3%)	41 (34%)
North America	1 (7.1%)	13 (11%)
South America	2 (14.3%)	5 (4%)
Australia and New Zealand	0 (0%)	5 (4%)
Africa	1 (7.1%)	7 (6%)
Therapeutic area		
Non-Communicable disease	12 (86%)	102 (85%)
Communicable disease	2 (14%)	18 (15%)
Covid-19[2]	1 (7%)	11 (9%)
Non-Covid-19	13 (93%)	109 (91%)
Complementary medicine[3]	10 (71%)	44 (37%)
Industry-sponsored[6]	3 (21%)	13 (11%)

[1] Some protocols were still awaiting ethical approval at the time of publication

[2] 71.EC_RCT_Gorman_May2022 [14] is partially Covid-19, therefore it was considered as Covid-19 and a communicable disease

[3] Complementary medicine: Is non-conventional therapy used alongside Western medicine (e.g., acupuncture, meditation, chiropractic care)

[4] Other: factorial, add-on, cluster and adaptive

[5] Other: include safety, mechanism of action, dose-finding and other miscellaneous purposes

[6] Trials funded by pharmaceutical companies

Discussion

Summary of findings

This is the first systematic review to examine the reporting practice around withholding established effective interventions in the protocols for placebo-controlled RCTs. In this review, placebo-controlled RCT protocols published in the journal *Trials* in 2022 were examined to determine the frequency of withholding established effective interventions without reported justification. We identified two related but distinct transparency issues in these trials: the absence of a clearly reported justification within the protocols themselves, and the absence of accessible participant-facing materials. With respect to the former, we identified that in about ten percent of the protocols an established effective intervention was

withheld (more commonly from both arms rather than just the control arm) without reported justification. With respect to the latter, the lack of available participant-facing material (e.g. consent forms) meant that it was not possible to identify whether participants were informed about an effective intervention being withheld, except in one case where we did have access to participant-facing material, we found no explanation was provided to the participants. We also identified that the practice of withholding effective interventions without a reported justification might be more common in RCTs conducted in Asia and those involving testing complementary and alternative interventions.

Example case studies

We examined whether the studies included in our review withheld effective interventions without *reporting* a justification, but this does not mean withholding an effective intervention is not justifiable. For example, one of the studies involved withholding doxycycline in the control arm of a trial of the treatment of ocular rosacea, a disease that can lead to vision loss. Here the authors quoted a previous placebo-controlled RCT showing that doxycline was effective in this condition [15]. However, this is not to say there might not be justification for withholding this intervention in this trial. For example, if there were problems with accessibility of the treatment in certain areas or if it was thought to be effective only in a certain population, these might be appropriate justifications for withholding doxycycline in this trial. In another example, a study of the treatment of patients with tuberculosis meningitis, aspirin was withheld from the control arm, despite reporting evidence of studies that aspirin reduces mortality rates in this condition in a similar population and setting [16]. Again, there may be a justification for withholding this intervention, but a justification was not reported.

Context and other literature

There is a rich literature on the different ethical considerations in RCTs [6]. For example, a systematic assessment of RCTs published between 2014 and 2018 showed that of the top 100 most widely cited RCTs, 8.8% did not obtain prospective informed consent from at least some research participants [14]. Others have considered the reported justifications for the use of a placebo—also finding that these justifications are often poorly reported [6]. There are also practical tools available, for example an algorithm to assist in determining if the use of a placebo is appropriate, including questions such as "is placebo being used in place of standard therapy?" and "is standard intervention considered to be effective?" [17].

Strengths and limitations

This review is the first to examine the issue of withholding established effective interventions without reporting a justification in placebo-controlled RCT protocols. The examination of multiple contextual factors could help generate some hypotheses as to which factors may be more likely to contribute to poor reporting of justifications for withholding established effective interventions.

There are some weaknesses with this review. This was a small study, restricted for practical purposes to a single year (2022) and a single journal, *Trials*. We believe the restriction to *Trials* is justified by the fact that this journal publishes a large proportion of RCTs and requires authors to adhere to the SPIRIT guidelines. However, restricting the sample to a single journal and a single calendar year limits the generalisability of these findings. In particular, caution is warranted when interpreting geographic patterns (e.g. the higher proportion of withholding protocols from Asia) and therapeutic-area differences, as these may reflect characteristics of the protocols submitted to *Trials* in 2022 rather than broader research practice. The findings of this review should therefore be regarded as hypothesis-generating rather than definitive. Additionally, protocols were limited to the English language, which further restricts the scope and generalisability of the findings.

Perhaps most importantly, we defined an intervention as "established effective" when the protocol authors themselves stated or cited evidence of its effectiveness, irrespective of the quality of that evidence. Importantly, we took the protocol authors' own word that the cited intervention was effective. This is acknowledged as a limitation of our approach. Moreover, assessing whether something as nuanced as "reporting a justification" is subjective. This was minimised by the use of a checklist to guide the assessment and classification of the included protocols to improve consistency in extractions, and having a second author (AG) review the classifications, with those identified as having poor reporting checked by a third author (KH). Whilst formal inter-rater reliability statistics (e.g. Cohen's kappa) were not calculated, all protocols flagged as potentially withholding an established effective intervention were discussed in detail between reviewers and disagreements were resolved by consensus, involving a third author (KH) where required. The absence of a formal reliability statistic is acknowledged as a limitation.

It is important to note that this study is not assessing whether the use of placebo or the withholding of an established effective intervention could *de facto* cause patient harm, but has assessed whether there was a reported justification for withholding established effective interventions. Further, it was found that provision

of participant-facing materials (e.g. consent forms) was poor, despite it being a requirement of the SPIRIT guidelines [5]. This makes it hard to assess whether patients are being fully informed about the potential for harm that might arise from their participation in a placebo-controlled RCT.

This study provides preliminary information on the extent of this problem. Given the small number of protocols identified as withholding effective interventions without justification (n = 14), the contextual associations reported, including the higher proportions observed in studies conducted in Asia and those testing complementary medicines, should not be over-interpreted as causal or definitive. These comparisons are exploratory and descriptive in nature and should be considered hypothesis-generating only. No formal sample size justification was undertaken for this review, which is an additional limitation. Further research could involve larger studies and longitudinal investigations to see how these patterns map over time. Reviews could also be performed of placebo-controlled RCTs that have been completed and published to evaluate whether they have the same issues, and also reviews could be performed on RCTs with an active comparison to assess whether effective concomitant treatments are withheld in both arms without justification. When justifications for withholding effective interventions are reported it would be also interesting to consider if these are consistent with criteria stipulated in international ethics guidelines [6]. Additionally, mandating submission of participant-facing materials as a journal requirement, for example, as supplementary files, could help address this issue and enable future reviews to assess more comprehensively the extent to which participants are well informed about their involvement in the study and its implications.

Conclusion

In this sample of protocols published in Trials in 2022, 10% (14/134) did not report a justification for withholding an established effective intervention. This represents a concerning proportion that warrants further attention, though the findings should be regarded as hypothesis-generating given they are drawn from a single journal and a single year. Furthermore, participant-facing materials are infrequently provided, preventing reviewers from assessing the extent to which research participants are informed of potential harms of study participation, particularly with respect to withholding of established effective interventions in placebo-controlled RCTs. Whilst we have identified some factors that seem to be associated with this poor reporting practice, further research is required to establish if these are true associations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-026-09897-9.

Additional file 1: S1. Checklist for identification of withholding known effective treatment in the placebo arm or concomitant medication that might be part of standard care.

Additional file 2: S2. Informed consent information of protocols not reporting a justification for with withholding effective interventions [18].

Additional file 3: S3. Characteristics of protocols identified as not reporting justification for withholding effective interventions [15, 16, 18–30].

Additional file 4: S4. Details of the issues from the protocols identified with withholding effective interventions and lifestyle restrictions [15, 16, 18–30].

Additional file 5: S5. Medline search terms.

Authors' contributions

AG led the development of the idea, screened the studies for inclusion, extracted outcomes and made a substantial contribution to the writing and revision of the manuscript. HA screened studies for inclusion, extracted data, devised the search criteria and wrote the first draft of the report. CEG and KH were responsible for revisions to subsequent drafts: KH made a substantial contribution to the writing of the abstract, methods and results; CEG made a substantial contribution to the writing of the abstract, introduction, methods and discussion. All authors approved the final version.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

AG receives funding from Trials journal to assist in reviewing protocols. KH was an editor at Trials journal at the time of the study.

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