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Original Article

Drug trials are more likely to disclose full placebo control information than non-drug trials: A cross-sectional study of participant information leaflets of placebo-controlled trials

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ABSTRACT

Background: This study aimed to investigate whether placebo control is differently disclosed in drug and non-drug randomised clinical trial (RCT) participant information leaflets (PILs) and how this might affect participant blinding and direction of study outcomes.

Methods: PILs were obtained from trials registered in the International Standard Randomised Controlled Trial Number database via email. Placebo descriptions in PILs were categorised as Full Disclosure (FD), Partial Disclosure (PD), or Missing Information (MI). Associations between intervention type (drug or non-drug)/placebo disclosure (FD or PD/MI) and participant blinding success/trial outcome direction (positive or non-positive) were examined using a two-sided Fisher's exact test.

Results: Of 116 collected PILs, 56 % were for drug trials and 44 % were for non-drug trials. Among them, 88 PILs had the corresponding publications available and 68 reports specified primary outcomes. Drug trials were more likely to fully disclose placebo information than non-drug trials (92.3 % vs. 74.5 %, $p < 0.05$). However, the success rate of blinding was only reported in 3 out of 88 trial publications (3.4 %), precluding further analysis. Furthermore, there was no significant association between the direction of trial results and the type of intervention or placebo disclosure.

Conclusion: Our study findings suggest that drug and non-drug RCTs might differ in the way they reveal placebo control information. Further research is warranted to understand what leads to more common PD of placebo information in non-drug trials than drug trials and to determine the optimal placebo control disclosure in specific trial context.

1. Introduction

In informed consent process in randomised clinical trials (RCTs), current standard is to fully disclose trial information, including placebo control, in participant information leaflets (PILs) to assist participants in making voluntary decisions.[1] While detailed study information helps participant autonomy, it has the potential to have unexpected consequences such as increased nocebo response[2] or negative impact on blinding.[3,4]

A valid placebo control should appear indistinguishable from the test intervention without its active component. In practice, however, an adequate placebo control is not always available even in drug trials,[5] and developing a valid placebo is known to be more challenging for non-pharmacological vs. pharmacological interventions.[6] Among various methods for maintaining blinding in non-drug RCTs such as sham procedures in surgical trials or attention-control in psychotherapy trials,[6,7] incompletely disclosing the study hypothesis and design is one strategy.[3,6] For example, in an RCT testing transcutaneous electrical nerve stimulation (TENS) against mock-TENS, the control arm patients were instructed that the treatment was high frequency and low intensity stimulation, so they would likely feel no sensation.[8]

Previous reports categorised types of placebo description in PILs into full disclosure (FD) and partial disclosure (PD): if a clear description of the placebo control is provided using such terms as "placebo", "sham", "dummy", or "fake", it was considered as FD; if placebo was not explicitly explained and inactiveness of placebo control could hardly be

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inferred, it was categorised as PD.[3,4] There have been some concerns about PD of placebo information in PILs for non-drug RCTs. Miller and Kaptchuk argued that in some acupuncture RCTs, participants were only informed that two different forms of acupuncture would be compared, without being told about the existence of a placebo control in the trial.[9] However, the above concerns were not derived from examining actual PILs but from a systematic review that only examined 10 acupuncture RCTs.[10] In a previous study examining placebo descriptions of 65 PILs from acupuncture RCTs,[3] more than half of the PILs were assumed to completely provide placebo information while the remaining PILs disclosed partial information about placebo control and studies with PD of placebo information were more likely to report larger effect sizes than FD trials. This study set out some grounds for a potential link between what trial participants are told about placebo control and participant blinding/direction of outcome.[3]

While above studies offered valuable insights for placebo disclosure in PILs, there remains a question whether placebo disclosures in PILs may differ between drug and non-drug RCTs. In this context, we aimed to investigate whether placebo is differently disclosed in drug and non-drug RCTs and how this might affect blinding and trial outcomes.

2. Methods

This study was approved by the Kyung Hee University Ethics Committee (KHSIRB-18–007).

2.1. Search strategy for trial registration datasets and PIL collection

Trial registration records in the International Standard Randomised Controlled Trial Number (ISRCTN) were searched in July 2018. Search strategy was to identify placebo-controlled RCTs completed between 2013 and 2017 using keywords of placebo OR sham. A primary contact person of trials identified in ISRCTN was asked via email to provide a full length PIL and if any, corresponding publications. Reminders were sent 10 and 20 days after the initial e-mail invitation. Language of PILs and trial phase were not restricted. In January 2019, an extended search was conducted in the same manner with the trials' completion year up to 2007, because some researchers responded they could not provide PILs as they were preparing for publication.

2.2. Data extraction and evaluation of placebo information disclosure in PILs

Languages other than English were translated into English with Google Translate. If corresponding publications were not provided with PILs, PubMed, Google Scholar, and Google were searched with the ISRCRN registry number. Information on general characteristics of the included RCTs was directly retrieved from the ISRCTN registry and analysed. Retrieved items were funder type (profit or non-profit), conditions/diseases, trial registration type (prospective or retrospective), and test intervention type (drug or non-drug). ISRCTN lists eight categories of intervention: behavioural, biologic/vaccine, device, drug, surgery/procedure, supplement, mixed, and others. Biologic/vaccine and drug were coded into drug, and behavioural, device, surgery/procedure, and supplement were coded into non-drug. If a PIL clarified a placebo control corresponding to a drug, mixed and others were classified into drug. For multinational trials, each country was counted separately. Disclosure types of placebo information in PILs were categorised into FD, PD, or missing information (MI) .[3] When placebo control was described as "placebo", "sham", "dummy", or "fake", which indicated physiologically inert nature to trial condition, or usage of placebo can be inferred from descriptions, these were considered as FD, eg., "You will be randomly assigned to either receive XXX or a similar looking placebo (sham drug)."; if placebo was explained as "the other treatment", "group two", or "control group" and inactiveness of placebo control could hardly be inferred, these were classified as PD, eg., "Some will receive traditional Korean acupuncture, and some will receive simple acupuncture treatment in a similar areas of the body. Control group will receive different stimulation maneuver at areas that are selected in the same way of experimental group."; and if there was no information about placebo control in PILs, these were categorised into MI. After two researchers independently evaluated placebo disclosure type, inconsistencies were resolved via discussion. PD and MI were combined as they did not completely disclose placebo control in common.

2.3. Association of placebo information disclosure in PILs with blinding and trial outcomes

To address the association of placebo information in PILs with blinding property, corresponding publications were checked whether the success of blinding was measured with a blinding index (BI) or BI calculation was available using reported information.[11] If the BI was identified or inferred, summed BI (summation of intervention group and placebo group BI) and blinding scenario was descriptively interpreted whether the study achieved ideal blinding.[12,13] Interpretation of BI, summed BI and blinding scenario are described in Supplement 1. Methodological factors such as random sequence generation, allocation concealment, and blinding of participants and outcome assessment that are known to influence the direction of study outcomes[13-17] were categorised into low, high, or unclear using the Cochrane risk of bias assessment tool.[18] As challenges in blinding of physicians or care givers can be different depending on the types of intervention (drug vs. non-drug), performance bias was evaluated not in blinding of researchers but in blinding of participants only.

Direction of trial results was judged to be positive or non-positive according to the statistical significance of primary outcomes only in parallel-group superiority trials in two ways: 1) If primary outcomes were more than one and all were statistically significant, they were considered as positive and otherwise non-positive. 2) If primary outcomes were more than one and one of them was statistically significant, this study was judged to be positive and otherwise non-positive. After the direction was determined, it was examined whether the types of interventions and the disclosure of placebo information, ie., FD PILs for drug RCTs (drug-FD), PD/MI PILs for drug RCTs (drug-PD/MI), FD PILs for non-drug RCTs (non-drug-FD), and PD/MI PILs for non-drug RCTs (non-drug-PD/MI), were related to the direction of outcome (positive vs. non-positive).

2.4. Statistical analysis

All statistical analyses were performed with R statistical software (version 4.3.1; R Core Team 2023). General characteristics of RCTs and PILs were reported descriptively: continuous variables were presented with mean ± 95 % confidence interval (CI) or median with interquartile range and categorical variables with number (%). A two-sided Fisher's exact test was used to examine: 1) whether there was a discrepancy in intervention type proportions (drug vs. non-drug) between the analysed PILs and those of the remaining of retrieved trial records from the ISRCRN registry to ensure representativeness of the PIL dataset; 2) whether the disclosure of placebo information (FD vs. PD/MI) differed between intervention types and odds ratio was presented with 95 % CI; 3) whether risk of bias (low, unclear, or high) in random sequence generation, allocation concealment, and blinding of participants and outcome assessment differed according to the disclosure of placebo information and intervention types; 4) whether the types of interventions and the disclosure of placebo information, ie., FD PILs for drug RCTs (drug-FD), PD/MI PILs for drug RCTs (drug-PD/MI), FD PILs for non-drug RCTs (non-drug-FD), and PD/MI PILs for non-drug RCTs (non-drug-PD/MI), were related to the direction of trial outcomes. Results of the exact test were considered statistically significant when p value was less than 0.05.

3. Results

3.1. Characteristics of the included PILs

The initial ISRCTN search yielded 664 records and additional search yielded 1220 records. Of 1884 datasets, 1200 records (63.7 %) had valid contact details available. Eligibility of 153 documents obtained (response rate: 12.8 %, 153 out of 1200), was checked and 116 PILs were subject to analysis of placebo disclosure types. Of them, 88 PILs had the corresponding publications and 68 parallel-group superiority RCT papers specified primary outcomes (Fig. 1).

The top four conditions were mental and behavioural disorders, infections and infestations, circulatory system diseases, and musculoskeletal disorders. Most trials (81 %) were supported by non-profit funders; more than half of them (53.8 %) recruited participants in the UK and 79.3 % of the obtained PILs were in English; and more than half of the included studies were retrospectively registered (59.5 %). The number of drug RCT PILs (65, 56.0 %) and non-drug RCTs (51, 44.0 %) was similar (Table 1). The proportions of intervention types (Supplement 2) did not statistically differ between the included PILs for 65 drug trials vs. 51 non-drug trials and the remaining 1768 records for which the PILs were not available (1022 drug trials vs. 746 non-drug trials, $p = 0.77$).

3.2. Placebo information disclosure in PILs for drug vs. non-drug RCTs

Placebo was fully disclosed in more RCT PILs (60/65, 92.3 %) than non-drug RCTs (38/51, 74.5 %). An example of FD was "… you will be randomly allocated to one of the following groups – either to OOO

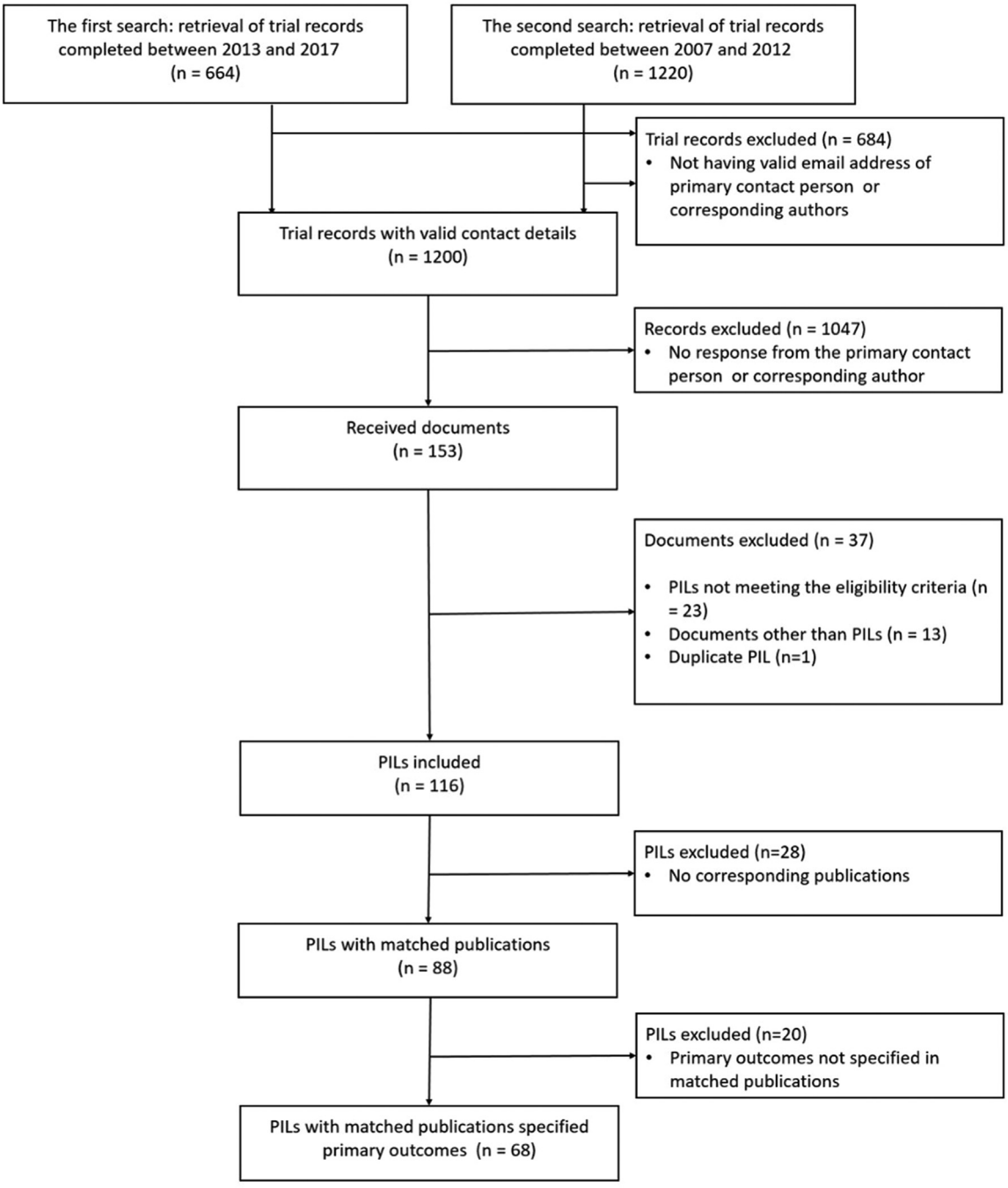

Fig. 1. Flow diagram of this study.

Table 1
Characteristics of the included trials with obtained PILs (n = 116).

	Drug trials (n,%)			Non-drug trials (n,%)			Total
	FD (n = 60)	PD/MI (n = 5)	Subtotal (n = 65)	FD (n = 38)	PD/MI (n = 13)	Subtotal (n = 51)	(n = 116)
Conditions							
Mental and behavioural	11 (18.4)	1 (20.0)	12 (18.4)	1 (2.6)	3 (23.1)	4 (7.8)	16 (13.8)
Infections and infestations	9 (15.0)	1 (20.0)	10 (15.4)	2 (5.4)	–	2 (3.9)	12 (10.3)
Circulatory system	5 (8.3)	1 (20.0)	6 (9.2)	4 (10.5)	1 (7.6)	5 (9.8)	11 (9.5)
Musculoskeletal system	2 (3.3)	1 (20.0)	3 (4.6)	7 (18.4)	1 (7.6)	8 (15.7)	11 (9.5)
Signs and symptoms	3 (5.0)	–	3 (4.6)	5 (13.2)	2 (15.5)	7 (13.8)	10 (8.6)
Nutritional, metabolic, or endocrine	3 (5.0)	–	3 (4.6)	2 (5.4)	3 (23.1)	5 (9.8)	8 (6.9)
Respiratory system	4 (6.7)	1 (20.0)	5 (8.0)	2 (5.4)	1 (7.6)	3 (5.8)	8 (6.9)
Others	23 (38.3)	–	23 (35.2)	16 (42.1)	2 (15.5)	18 (35.2)	40 (34.5)
Funder							
Profit	9 (15.0)	2 (40.0)	11 (16.9)	8 (21.1)	3 (23.1)	11 (21.6)	22 (19.0)
Non-profit	51 (85.0)	3 (60.0)	54 (83.1)	30 (78.9)	10 (76.9)	40 (78.4)	94 (81.0)
Target number of participants	180 [100, 446]	297 [100, 360]	180 [100, 446]	100 [54, 254]	44 [31, 58]	80 [50, 95]	130 [60, 326]
Country of recruitment*							
UK	42 (70.0)	4 (80.0)	46 (70.8)	20 (52.6)	5 (35.7)	25 (49.0)	71 (53.8)
Netherlands	4 (6.7)	–	4 (6.2)	3 (7.9)	1 (7.1)	4 (7.8)	8 (6.1)
Canada	3 (5.0)	–	3 (4.6)	3 (7.9)	1 (7.1)	4 (7.8)	7 (5.3)
Sweden	3 (5.0)	–	3 (4.6)	4 (10.5)	–	4 (7.8)	7 (5.3)
Others	14 (23.3)	1 (20.0)	15 (23.1)	17 (44.7)	7 (50.0)	24 (47.1)	39 (29.5)
Language of PILs							
English	49 (81.7)	3 (75.0)	52 (81.3)	28 (71.8)	8 (88.9)	36 (75.0)	88 (79.3)
Dutch	4 (6.7)	–	4 (6.2)	2 (5.1)	–	2 (4.2)	6 (5.4)
German	2 (3.3)	–	2 (3.1)	3 (7.7)	1 (11.1)	4 (8.3)	6 (5.4)
Swedish	2 (3.3)	1 (25.0)	3 (4.7)	3 (7.7)	–	3 (6.3)	6 (5.4)
Others	3 (5.0)	–	3 (4.7)	3 (7.7)	–	2 (4.2)	5 (4.5)
Trial registration type							
Prospective	31 (51.7)	–	31 (47.6)	14 (36.8)	2 (15.4)	16 (31.4)	47 (40.5)
Retrospective	29 (48.3)	5 (100.0)	34 (52.4)	24 (63.2)	11 (84.6)	35 (78.6)	69 (59.5)

Data are presented with n (%) except target number of participants which is presented with median [first quartile, third quartile].
* Of the included PILs, four trials recruited participants from more than one country.
FD, full disclosure; MI, missing information; PD, partial disclosure; PILs, participant information leaflets.

administered or placebo. A placebo is also called a 'dummy' as it contains no active medication." The proportion of PD of placebo was 6.2 % (4/65) and 21.6 % (11/51) for drug RCTs and non-drug RCTs, respectively. Typical statements of PD include "There are two different types of meditation being investigated and to ensure control and rigour, neither the participants nor the researchers will be aware of which condition any individual participant is in …" One PIL for drug RCT and two PILs for non-drug RCTs were categorised into MI, ie., no mentioning of placebo controls (Supplement 3).

PILs for drug RCTs were more than 4 times likely to completely disclose placebo control compared to PILs for non-drug RCTs (odds ratio: 4.05; 95 % CI: 1.45 – ∞; $p < 0.05$ by Fisher's exact test). Among 7 intervention categories included in the analysis, ie., behavioural, device, drug, surgery/procedure, supplement, mixed, and others, all 3 studies of behavioural intervention had PILs with PD and 15 studies of supplement all had PILs with FD. The proportion of FD PILs was higher in all the other intervention studies ($p < 0.0004$).

3.3. Reporting of blinding and risk of bias assessment according to intervention types and placebo information disclosure

Of 88 papers that paired with corresponding PILs, seven studies (three drug-FD trials and four non-drug FD trials) reported that they evaluated the success of participant blinding. Of them, only three studies (two drug trials one non-drug trial) provided the details for BI calculation Supplement 1). There was no significant difference between reporting blinding assessment in drug vs. non-drug trials ($p > 0.05$ by Fisher's exact test, Table 2).

Most risk of bias items were judged as low or unclear and no high risk of bias was given: blinding of participants was assessed as low irrespective of intervention and placebo disclosure types because all studies used placebo or sham as a control. Results of Fisher's exact test to determine whether risk of bias differed depending on the intervention types and placebo information disclosure (Table 2), indicated that blinding of outcome assessment was statistically different between drug and non-drug, ie., drug studies were more likely to be judged as having low risk of bias than non-drug studies ($p = 0.01$). No significant association emerged in other domains.

3.4. Association of placebo disclosure in PILs with direction of the study outcomes

Of 68 parallel-group superiority RCTs specifying primary outcomes in publications, 10 studies (14.7 %) reported positive results. Of them, seven drug trials (16.3 % out of 43 drug-FD publications) used FD PILs; two studies were non-drug-FD publications; the remaining one non-drug study adopted PD/MI PILs. The direction of primary outcomes (positive vs. non-positive) was consistent irrespective of the ways determining it and did not significantly differ by the type of intervention and disclosure status of placebo ($p = 0.38$, Fig. 2).

4. Discussion

In the informed consent process, sufficient and adequate information should be provided in PILs to facilitate truly informed decisions.[1] However, some medical ethicists argue that some non-drug RCT researchers are reluctant to completely disclose research hypothesis to participants and only partially disclose the use of placebo probably out of concern for unblinding. To the best of our knowledge, there has been no study that verified whether such suspicions were true. By analysing the contents of actual PILs obtained from the clinical trialists, we examined whether degree of placebo information disclosure in PILs differ between drug and non-drug trials. Our key results suggest that PILs for drug RCTs were more than 4 times likely to provide full details of placebo control information compared to PILs for non-drug RCTs.

Table 2
Blinding assessment and risk of bias in papers with PILs in drug vs. non-drug trials (n = 88).

	Drug trials (n,%)			Non-drug trials (n,%)			Total
	FD (n = 52)	PD/MI (n = 3)	Subtotal (n = 55)	FD (n = 26)	PD/MI (n = 7)	Subtotal (n = 33)	(n = 88)
Blinding assessment							
Yes	3 (5.8)	–	3 (5.5)	4 (15.4)	–	4 (12.1)	7 (8.0)
No	49 (94.2)	3 (100.0)	52 (94.5)	22 (84.6)	7 (100.0)	29 (87.9)	81 (92.0)
Risk of bias items							
Random sequence generation							
Low	48 (92.3)	2 (66.7)	50 (90.9)	23 (88.5)	5 (71.4)	28 (84.8)	78 (88.6)
Unclear	4 (7.7)	1 (33.3)	5 (9.1)	3 (11.5)	2 (28.6)	5 (15.2)	10 (11.4)
Allocation concealment							
Low	46 (88.5)	2 (66.7)	48 (87.3)	20 (76.9)	4 (57.1)	24 (62.8)	72 (81.8)
Unclear	6 (11.5)	1 (33.3)	7 (12.7)	6 (23.1)	3 (42.9)	9 (27.2)	16 (18.2)
Blinding of participants							
Low	52 (100.0)	3 (100.0)	53 (100.0)	26 (100.0)	7 (100.0)	35 (100.0)	88 (100.0)
Unclear	–	–	–	–	–	–	–
Blinding of outcome assessment							
Low	52 (100.0)	2 (66.7)	54 (98.2)	24 (92.3)	5 (71.4)	29 (87.9)	83 (94.9)
Unclear	–	1 (33.3)	1 (1.8)	2 (7.7)	2 (28.6)	4 (12.1)	5 (5.7)

Data are presented with n (%).
FD, full disclosure; MI, missing information; PD, partial disclosure; PIL, participant information leaflet.

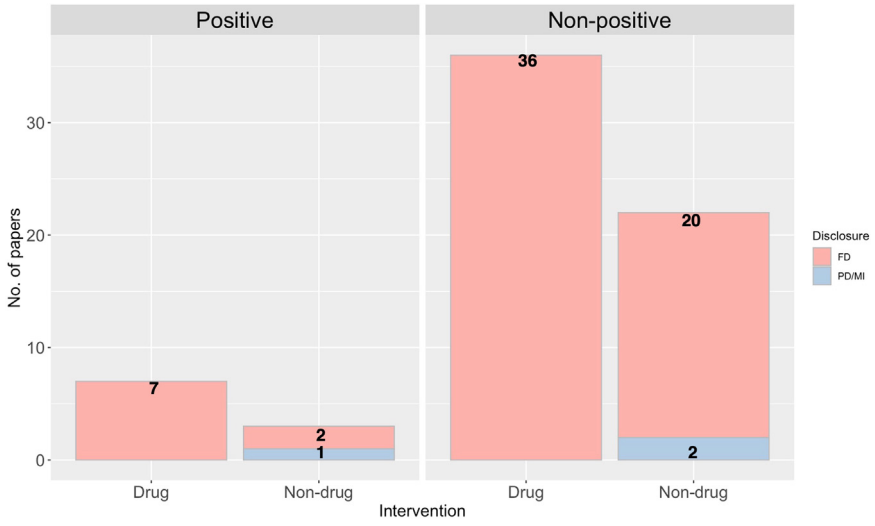

Fig. 2. Association of placebo disclosure in PILs with direction of the study outcomes in drug vs. non-drug trials.
FD, full disclosure; MI, missing information; PD, partial disclosure; PIL, participant information leaflet.

Blinding has been reported less frequently in RCTs assessing non-phamacological treatment possibly due to challenges in achieving and maintaining it and also a lack of knowledge about existing methods in the field.[19,20] This is consistent with results of this study. Only seven studies (8.0 %) out of 88 publications with available PILs, reported that blinding assessment was done. Of them, only three studies (3.4 %) had BI calculations available, hence it was not feasible in this study to determine whether the placebo disclosure affected participant blinding. Such a low rate of reporting blinding success is similar to the findings from previous studies where the rate of reporting patient blinding evaluation was only 5.6 % and 7 % of the included trials, respectively.[19,20] It is not clear if this means the blinding assessment was not performed during the trial or the results of blinding assessment were not reported in the publications. While an item regarding reporting of blinding assessment was eliminated in COnsolidated Standards of Reporting Trials (CONSORT) 2010 guideline,[21] such poor reporting practices make it more challenging to adequately evaluate and interpret the study findings. A recently published guideline for reporting placebo controls requires reporting of blinding assessment and this may be a game changer to promote reporting participant blinding evaluation if it is widely endorsed.[22]

There was no significant association of intervention type and placebo disclosure in PILs with the direction of study results in 68 superiority trials. This is inconsistent with the previous studies[3] that reported PD/MI of sham acupuncture information was associated with greater acupuncture effect[3] and variations in the effect of placebo were partly explained by variations in how patients were informed about the possible placebo intervention.[23] Larger effect sizes in PD/MI trials could be interpreted as a result of increased expectations under PD/MI circumstances due to not knowing about the possibility of receiving sham acupuncture. Because of substantial heterogeneity in interventions of the included studies and accordingly study characteristics, the impact of placebo information disclosure on expectation and direction of trial results of the present study may differ from those in that study.

One interesting, but almost overlooked, result is that we had far fewer studies with positive outcomes than expected relative to those with non-positive outcomes (10 vs. 58), to the contrary to commonly acknowledged phenomenon of publication bias. There can be a couple of reasons for this unpredictable finding: first of all, our criteria to determine positive vs. non-positive results might be too strict as direction of trial results was based on the pre-specified primary outcomes and if there were more than one primary outcomes, we considered it to be positive only when all primary outcomes were statistically different. However, classifying studies with any one significant primary outcome into positive category did not alter the analysis. Secondly, the

included studies were all placebo-controlled, and a variety of factors such as the type of placebo, outcome measures, the conditions or diseases under scrutiny, and size of trials, can influence the variability in placebo effects.[23] Variable placebo effects may have affected the effect size of the included trials and led to an unexpectedly high proportion of non-positive studies. Last but not least, we can suspect researchers of trials with positive results may be more reluctant to share their methodologies or documents with unknown reasons and this issue needs further investigation.

To the best of our knowledge, this is the first study that compared PILs for drug and non-drug RCTs with regard to placebo disclosure along with its possible influence over participant blinding and trial outcomes. Our results confirm what some medical ethicists have feared,[9] albeit unsupported, by analysing PIL descriptions, showing there was a clear trend toward less complete disclosure of placebos in non-drug studies than in drug studies. While developing and implementing a valid placebo control can be more challenging for non-drug vs. drug treatments and somewhat deceitful disclosure of placebo control or research hypothesis to potential participants has been used as one of the strategies for securing blinding,[6] the actual reasons for the reluctance to fully disclose placebos in non-drug studies have not received as much attention as they should. One RCT specifically tested the impact of FD and PD on blinding and trial outcomes, and PD was acceptable to most participants after debriefing.[4] Further investigation is warranted to identify the best ways to disclose placebos to inform participants without endangering their autonomy and while maintaining blinding to ensure study rigour and validity. In this sense, the present findings may serve as a good starting point to explore and improve what trial participants are told about placebo control.

This study has some drawbacks. First, response rate of providing PILs was low (12.8 %). In our study, PILs were requested via email of primary contact persons collected from the ISRCTN registry and corresponding authors of publications were additionally invited. E-mail request is probably the only method to collect PILs from the trialists, yet this approach may have some inherent limitations leading to a poor response rate. If published placebo controlled RCTs were searched in the databases such as PubMed and corresponding authors were invited via email to provide their PILs, response rate might have slightly increased. However, as we aimed to collect any PILs irrespective of publication status, primary contact persons were e-mailed based on datasets in the ISRCTN registry. Accordingly, to check the representativeness of collected PILs, the proportion of intervention type of the included PILs was compared to that of entire trial registration datasets and no noticeable heterogeneity was observed. Second, the proportion of PD/MI PILs (18 out of 116 RCTs, 15.5 %) might be underestimated if primary contact persons of PD/MI PILs judged their PIL contents could be problematic and thus were reluctant to share their PILs. We cannot be entirely sure if the analysed PD/MI PILs were adequate to serve as a representative sample. Third, as our primary goal was to determine whether there was discrepancy in placebo disclosure in PILs between drug and non-drug RCTs, the impact of potential variables other than intervention type was not further investigated. Possible variables include varying regulations about informed consent and disclosure across countries and institutions, double-blind trial testing device-based treatments where patient unblinding during the trial was inevitable without a lack of FD,[24] or different sociocultural familiarity with the testing interventions such as acupuncture in East-Asian countries.[25] Also, the actual understanding of the placebo information on PIL by participants may not be in accordance with degree of information disclosure in this study.

Our study findings suggest that drug and non-drug RCTs differ in degree to which placebo control information is disclosed. Further research is warranted to understand what leads to more prevalent PD of placebo information in non-drug trials than drug trials and to determine the optimal placebo control disclosure in specific trial context. Because it was not determined in this study whether placebo disclosure affects participant blinding and/or trial results mainly due to a paucity of reported data, a thorough reporting of blinding assessment in future studies is needed. Given that PILs are used in most of clinical trials and modification of them hardly requires additional cost and resources, changes in the descriptions of placebo control in PILs will be readily made if deemed necessary. Because we have relatively few empirical studies on optimal placebo control disclosure across various disciplines, more research is needed to determine whether the present findings are also applicable to other areas of medical research.

CRediT authorship contribution statement

Jiyoon Won: Investigation, Writing – original draft, Formal analysis. **Ji-Yeon Han:** Validation, Writing – review & editing. **Yu-jin Ji:** Validation, Writing – review & editing. **Dohyung Ha:** Validation, Writing – review & editing. **Bong Jae Han:** Validation, Writing – review & editing. **Hyangsook Lee:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing, Supervision.

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Conflict of interest

The authors have no conflict of interest to declare.

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Ethical statement

This study was approved by the Kyung Hee University Ethics Committee (KHSIRB-18-007).

Data availability

The data will be made available upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2024.101043.

References

1. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194. doi:10.1001/JAMA.2013.281053.
2. Wells RE, Kaptchuk TJ. To tell the truth, the whole truth, may do patients harm: The problem of the nocebo effect for informed consent. *Am J Bioeth*. 2012;12(3):22–29. doi:10.1080/15265161.2011.652798.
3. Cheon S, Park HJ, Chae Y, Lee H. Does different information disclosure on placebo control affect blinding and trial outcomes? A case study of participant information leaflets of randomized placebo-controlled trials of acupuncture. *BMC Med Res Methodol*. 2018;18(1):13. doi:10.1186/s12874-018-0474-1.
4. Won J, Bang H, Lee H. Effect of partial vs full disclosure of potential assignment to placebo on participant blinding, perceptions of group assignment, and trial outcomes: a randomized clinical trial. *JAMA Netw Open*. 2022;5(3):e224050. doi:10.1001/JAMAnetworkopen.2022.4050.
5. Bello S, Wei M, Hilden J, Hróbjartsson A. The matching quality of experimental and control interventions in blinded pharmacological randomised clinical trials: a methodological systematic review. *BMC Med Res Methodol*. 2016;16:18. doi:10.1186/s12874-016-0111-9.
6. Boutron I, Guittet L, Estellat C, Moher D, Hróbjartsson A, Ravaud P. Reporting methods of blinding in randomized trials assessing nonpharmacological treatments. *PLoS Med.*. 2007;4(2):e61. doi:10.1371/journal.pmed.0040061.

7. Hróbjartsson A, Boutron I. Blinding in randomized clinical trials: imposed impartiality. *Clin. Pharmacol. Ther.*. 2011;90(5):732–736. doi:10.1038/clpt.2011.207.
8. Lewith GT, Prescott P, Davis CL. Can a standardized acupuncture technique palliate disabling breathlessness: a single-blind, placebo-controlled crossover study. *Chest*. 2004;125(5):1783–1790. doi:10.1378/chest.125.5.1783.
9. Miller FG, Kaptchuk TJ. Acupuncture trials and informed consent. *J Med Ethics*. 2007;33(1):43–44. doi:10.1136/jme.2006.016535.
10. Linde K, Dincer F. How informed is consent in sham-controlled trials of acupuncture? *J Altern Complement Med*. 2004;10(2):379–385. doi:10.1089/107555304323062374.
11. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25(2):143–156. doi:10.1016/j.cct.2003.10.016.
12. Moroz A, Freed B, Tiedemann L, Bang H, Howell M, Park JJ. Blinding measured: a systematic review of randomized controlled trials of acupuncture. *Evid Based Complement Alternat Med*. 2013;2013:708251. doi:10.1155/2013/708251.
13. Freed B, et al. Blinding, sham, and treatment effects in randomized controlled trials for back pain in 2000-2019: a review and meta-analytic approach. *Clin Trials*. 2021;18(3):361–370. doi:10.1177/1740774520984870.
14. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273(5):408–412. doi:10.1001/JAMA.273.5.408.
15. Odgaard-Jensen J, et al. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2011;2011(4):Mr000012. doi:10.1002/14651858.MR000012.pub3.
16. Savović J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. *Health Technol Assess*. 2012;16(35):1–82. doi:10.3310/hta16350.
17. Pildal J, Hróbjartsson A, Jørgensen KJ, Hilden J, Altman DG, Gøtzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol*. 2007;36(4):847–857. doi:10.1093/ije/dym087.
18. Higgins JP, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi:10.1136/bmj.d5928.
19. Fergusson D, Glass KC, Waring D, Shapiro S. Turning a blind eye: the success of blinding reported in a random sample of randomised, placebo controlled trials. *BMJ*. 2004;328(7437):432. doi:10.1136/bmj.37952.631667.EE.
20. Colagiuri B, Sharpe L, Scott A. The blind leading the not-so-blind: a meta-analysis of blinding in pharmacological trials for chronic pain. *J Pain*. 2019;20(5):489–500. doi:10.1016/j.jpain.2018.09.002.
21. Schulz KF, Altman DG, Moher D, Fergusson D. CONSORT 2010 changes and testing blindness in RCTs). *Lancet*. 2010;375(9721):1144–1146. doi:10.1016/s0140-6736(10)60413-8.
22. Howick J, et al. TIDieR-Placebo: a guide and checklist for reporting placebo and sham controls. *PLoS Med*. 2020;17(9):e1003294. doi:10.1371/journal.pmed.1003294.
23. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochran Datab Syst Rev*. 2010;2010(1):Cd003974. doi:10.1002/14651858.CD003974.pub3.
24. Djavadkhani Y, et al. Ethics, consent and blinding: lessons from a placebo/sham controlled CPAP crossover trial. *Thorax*. 2015;70(3):265–269. doi:10.1136/thoraxjnl-2014-206354.
25. Volinn E, Yang B, He J, Sheng X, Ying J, Zuo Y. Do outcomes of acupuncture for back pain differ according to varying sociocultural contexts? The view from China. *J Altern Complement Med*. 2013;19(5):435–444. doi:10.1089/acm.2010.0786.