

Recommendations for the Development, Implementation, and Reporting of Control Interventions in Efficacy and Mechanistic Trials of Physical, Psychological, and Self-Management Therapies - The CoPPS Statement.

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Short summary

Control interventions, often called “sham”, “placebo” or “attention controls”, are essential for studying the efficacy or mechanism of physical, psychological, and self-management interventions in clinical trials. This article presents core recommendations for designing, conducting, and reporting control interventions to establish a quality standard in non-pharmacological intervention research. A framework of additional considerations supports researchers’ decision-making in this context. We also provide a reporting checklist for control interventions to enhance research transparency, usefulness, and rigour.

Summary points

- The design, conduct, and reporting of control interventions are fundamental for interpreting efficacy and mechanistic clinical trials of physical, psychological, and self-management interventions.
- We developed this guideline using a three-round Delphi study with 64 experts in placebo research and/or clinical trials. This panel was presented with a systematic review of control and blinding methods and a meta-analysis that linked design features to trial endpoints. Consensus items informed interviews with patient partners. Finally, 44 Delphi participants and 2 patient representatives discussed the draft manuscript and results from stakeholder interviews at online consensus meetings.
- For clinical trials of treatment efficacy or mechanisms, we recommend designing control interventions that are as similar as possible to the tested intervention, apart from the components examined by the study.
- Structured planning, early stakeholder engagement, feasibility work, and piloting will improve the quality and acceptability of control interventions.
- When participant blinding is an objective, blinding effectiveness should be routinely assessed and reported.
- Detailed and transparent reporting will improve the interpretation and repeatability of clinical trials.

Introduction

Randomised controlled trials (RCTs) that test the efficacy of a drug against a so-called “placebo control” are well-established in drug research. In principle, “placebo controls” mimic the treatment under investigation, but lack its supposed active ingredient,[1] for example, as pharmacologically inert sugar pills or saline injections. Such specifically designed control interventions control for the natural history of the disease and regression to the mean. Importantly, these interventions also account for context-dependent effects, such as those produced by patient–provider interactions and treatment-related rituals. Researchers can use such interventions to blind trial participants, treatment providers, and outcome assessors to trial participants’ group allocation, concealing whether the investigational treatment or the control is administered. Through the indistinguishability of drug and control, all trial participants are exposed to similar treatment contexts, which should lead to comparable expectations of treatment benefit.

In non-pharmacological trials, methodological criticism of control interventions (often called “sham” controls, representing the equivalent of placebo controls) contributes to concerns about research quality.[2–7] Ultimately, these concerns impede adequate consideration of many therapies for clinical guidelines or reimbursement. Whilst some of these concerns are due to a lack of methodological guidance on the use of control interventions, others stem from a failure to consider the nature of non-pharmacological trials and its impact on control methods. For example, a sometimes unavoidable lack of therapist blinding leads to a downgrading on the PEDro scale,[8] a commonly used risk-of-bias scale in physiotherapy research, irrespective of other valid attempts to mitigate related bias risks.

Efficacy trials help to understand intervention effects in experimental or ideal settings. Such trials are important to study intervention mechanisms and causal effects on outcomes. In a pluralistic framework of complex intervention research (such as the 2021 Medical Research Council guidance for complex intervention development and evaluation), efficacy trials complement research designs that are more implementation-focused.[9] Although a central feature of efficacy trials, existing guidance for control intervention design focuses on individual therapies, such as psychotherapy,[10] behavioural interventions,[11] rehabilitation,[12] sports and exercise,[13] physiotherapy,[14] and manual therapy.[15] These guidelines provide no quality checklist and few generalisable principles; moreover, they often disregard problems of intervention complexity.[9] Consequently, various fields follow different approaches to fundamental questions of control intervention design, such as how closely the control should resemble the study intervention. Whilst there is a trend towards high-similarity controls in some research areas (notably spinal manipulation), in other areas (e.g., other physical therapies and psychological therapies), control interventions often do not resemble the study treatments or efficacy trials are avoided altogether.[16,17] A lack of consensus on relevant issues exposes the field to justifiable criticism due to concerns over bias [18–22] and leaves questions of treatment mechanism unanswered. Finally, the only *reporting* checklist for control interventions is the Template for Intervention Description and Replication for placebo and sham controls (TIDieR-Placebo), developed for both drug and non-drug studies. However, it may not be sufficiently comprehensive to reflect the challenges of control interventions in all types of physical, psychological, and self-management (PPS) intervention efficacy trials.

To fill this gap in guidance, we here present Recommendations for the Development, Implementation, and Reporting of Control Interventions in Efficacy and Mechanistic Trials of Physical, Psychological, and Self-Management Therapies - The CoPPS Statement. This guidance is dedicated to PPS interventions, which present unique challenges for blinding and control interventions. The PPS term includes all forms of manual and physical therapy, exercise and rehabilitation therapy, conversation-based and psychological therapies, mind–body, spiritual, religious, and other non-material healing practices, and educational interventions. We will not consider surgical, needle-based, or meridian interventions, devices, drugs, or nutritional interventions in this discussion, as there are alternative options for creating “sham” controls (e.g., treatment under anaesthesia, use of non-acupuncture points, or device deactivation). Importantly, this guidance is intended for researchers who have decided that a controlled efficacy or controlled mechanistic RCT is appropriate for their research question. Conceptualising clinical research as a spectrum from explanatory to pragmatic,[23,24] the control interventions discussed here are more useful for reducing bias when testing the efficacy of a given intervention or for studying mechanisms of action rather than estimating an intervention’s effectiveness under real-world conditions. Thus, these guidelines are more appropriate for trials on the explanatory end of the explanatory–pragmatic continuum. We caveat that each clinical trial is different. Specific solutions will be informed as much by the present guidance as by the uniqueness of the treatment and population under investigation, the research question, and practical considerations. The adoption of all recommendations may not always be feasible or desirable. We encourage researchers to consider each recommendation carefully, assess its relevance and feasibility for their present research project, and justify their decision in the trial protocol, report, or supplement. We also highlight scenarios in which individual recommendations may be particularly important (also see supplementary explanations and elaborations document).

Methods

We have based our statement on a systematic review of methods,[17,25] a three-round Delphi study,[26] interviews with patient partners, and consensus meetings.[27] Methods were adapted from available best-practice guidance for guideline development[27] and relevant, related publications[28], notably adding patient involvement and the consultation of placebo research experts to the methodology. A detailed protocol of the consensus process was prospectively registered on the Open Science Framework (<https://osf.io/jmyhq/>), where a detailed documentation of this project's methods and results is also available (Supplements 1a, 1b, and 2). The study was approved by the Imperial College Institutional Review Board (study no. 21IC6668). The scope of this guideline is PPS interventions, excluding surgery, acupuncture, and devices.

The systematic review identified current methodological and reporting practices in relevant trials [17] and our meta-analysis showed that control intervention design influences trial outcomes.[25] The first Delphi questionnaire was informed by these insights as well as earlier relevant literature on control design and blinding (e.g., [10,12,29–31,14]). A total of 68 experts in placebo research and clinical trials of PPS interventions received the round-one Delphi questionnaire, of which 48 completed round three (71% retention). During the Delphi, experts indicated their level of agreement to potential recommendation items for this guideline, provided additional considerations in response to open-ended questions, and received feedback about other panellists' ratings between each round. After the Delphi stage, eight lay persons with present or past experiences of long-term pain were interviewed about the proposed recommendations. We recruited these individuals through patient advocacy networks. Draft guidance was then discussed at a series of online meetings with the same Delphi panellists (n = 44) and two of the same lay people living with persistent pain, who had volunteered to participate. Apart from being subject experts, several individuals from the panel and author group had experience in guideline development. The guideline development process is illustrated in Figure 1 and described in detail in Supplement 1a. The preparatory systematic literature review and meta-analysis have been published.[17,25]

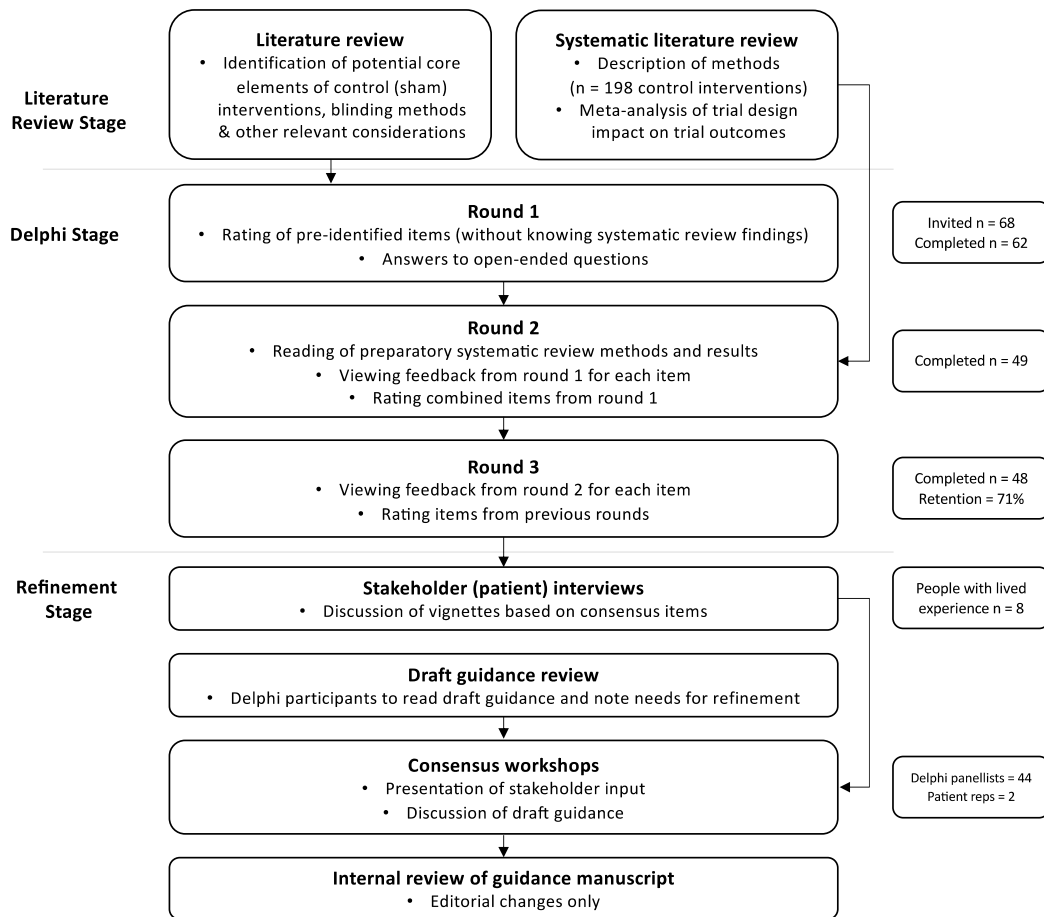


Figure 1: Flowchart of the guidance development process.

The guidance presented in this article includes items that reached consensus at the Delphi stage (for detailed results per item, see Supplement 1b). The CoPPS Checklist provides a summary of essential recommendations, representing quality standards that are required of any control intervention in a PPS trial (Table 1). In addition to reaching consensus in the Delphi stage, these items were seen as applicable and essential to all controlled efficacy and mechanistic trials of PPS interventions, and were selected during online consensus meetings and manuscript writing. During this project, most discussions and Delphi items concerned the development and implementation of control interventions. However, recommendations for reporting items were also made, which were added to an existing reporting checklist[32] to ensure that readers have easy access to all relevant guidance for control interventions in PPS trials.

For readers desiring further detail or wishing to apply the CoPPS Statement in their trial, an Explanations and Elaborations (E&E) document provides additional considerations and practical examples to guide researchers in the decision-making process. The E&E document, an editable version of the CoPPS Checklist of essential recommendations, and an editable version of a

dedicated reporting checklist are available as “toolbox” supplements, helping researchers to apply the main statement’s recommendations.

Guidance statement

As part of the CoPPS statement, we specify important terminology, provide general considerations for control interventions in efficacy trials, present fundamental principles for the conceptual development of control interventions, and discuss key aspects of their piloting and their implementation in clinical trials, their evaluation, reporting, and the interpretation of trial results. A checklist of core recommendations for the development and implementation of control interventions in efficacy and mechanistic trials of PPS interventions is presented in Table 1 (An editable checklist is available as supplement, which we recommend is used by trialists). The guidance statement is displayed visually in Figure 2.

Table 1: CoPPS Checklist for the development and implementation of a control intervention in efficacy and mechanistic trials of physical, psychological, and self-management interventions.* We recommend that trialists use this checklist to document their decision-making and describe how each recommendation was implemented in their specific trial. For this purpose, a modifiable version of this checklist is available as supplement.

CoPPS section	Essential recommendation item
<i>Design and development stage</i>	
2.3.	Consider ethical arguments for and against performing an efficacy or mechanistic trial with a control intervention, including from the perspective of a trial participant.
2.1. & 3.1.	Clearly define the objectives of the control intervention in the context of the research question at hand. (This is to include considerations of the blinding of any involved parties.)
3.1.	Perform a literature review of comparable control interventions and their available blinding data.
3.1.	Define the mechanism(s) of interest of the test intervention.
3.1.	Specify the components of the test intervention thought to act on the above mechanism(s).
2.1. (Also see Table 3 for a list of influential components)	The control intervention should replicate as many components of the investigated treatment as possible, apart from the components whose effect the trial aims to study.
2.1.	Ensure that the control intervention is inert for the studied mechanism(s) and does not include the component(s) of interest.
3.2.	Test the control intervention in a feasibility or validation step, ensuring that certain quality criteria are met.

(Note the quality criteria and additional suggestions in sections 3.2. & 3.3.)	
3.2.	Consider and mitigate, if required, the risk of group contamination.
2.1. & 3.3. (Also note Table 3)	Providers should be specifically trained to deliver the control intervention (if applicable).
3.3.	Staff (not just treatment providers) must be educated to recognise the importance of maintaining effective blinding (if applicable).
3.4.	Outcome assessors must be blinded.
3.4.	The roles of treatment providers and outcome assessors must be separated if providers cannot be blinded.
3.4.	Statistical analyses must be blinded.
<i>Trial conduct stage</i>	
4.1.	Providers' fidelity to intervention protocols and scripts should be monitored (if applicable).
4.1.	Participants' adherence to and compliance with intervention protocols should be monitored (if applicable).
4.2.	Provider expectations of benefit from the control versus the test treatment should be evaluated (if applicable).
4.2.	Participants' expectations of treatment benefit should be assessed at baseline and after starting treatment sessions.
4.2	Participant blinding must be assessed (if applicable).
4.3	Reasons for participants' withdrawal from the study should be documented.

* The checklist items represent a core of best-practice recommendations that apply in any controlled efficacy or mechanistic trial of PPS interventions. The checklist complements the broader decision-making framework presented in this publication and its supplementary Explanations & Elaborations document. Column 1 refers to these publications' respective sections for further information about individual items.

Recommendations for the Development, Implementation, and Reporting of Control Interventions in Efficacy Trials of Physical, Psychological, and Self-Management Therapies

THE COPPS STATEMENT

SCOPE

For research questions requiring a mechanistic or efficacy randomized control trial with a specifically designed control interventions (sometimes called 'sham' or 'placebo control').



References of original publication, TIDieR-P, and our systematic review

Figure 2: Graphical illustration of the CoPPS statement.

1. Terminology and communication

In non-pharmacological trials, the terms “sham” or “attention control” are commonly used instead of “placebo.” None of these terms are ideal: “Sham” may be associated with deceit and has been thought to undermine trust in the research by consulted patient representatives. “Attention control” is too restrictive, applying only to one component of an experimental treatment, the “attention” from the healthcare system. “Placebo” has a negative connotation, does not acknowledge the potential for direct benefits of control treatments, and has various interpretations among the public. Thus, we encourage the use of *simplified terminology* and *descriptive language*, both when reporting research methods within the scientific community and in communication with (potential) trial participants and providers (see Table 2). For example:

“The control is the same as the tested treatment, except that one component has been removed. In this trial, we test the effects of this component.”

Or: “The tested treatment consists of multiple components. The trial’s aim is to study the effect of some of these components. To do so, the test treatment is compared with a control that has all of the original components except those components that the trial aims to study.”

If formally required, *after explaining the concept*, one may wish to add that this control intervention is sometimes referred to as “sham” or “placebo control.” Importantly, this approach will enable enhanced communication in all languages and can be adapted to different audiences, ideally guided by stakeholder involvement.

Table 2: Glossary of relevant terms. The following definitions have been agreed upon as part of a consensus-finding process and form the basis of wording in the guidance document. These terms represent a deliberate simplification of language and omit commonly used terms that are considered unhelpful (notably “sham” and “placebo”). We encourage researchers to adopt similar language in their communications with colleagues and members of the public. This guidance focuses on the scope of therapies given by the definition of PPS therapies, as further justified in the text.

<p>Control intervention (in the context of efficacy or mechanistic trials)</p>	<p>Definition: Procedures delivered to trial participants in the control group, specifically designed to test the efficacy or mechanism of the test intervention.</p> <p>These control interventions are distinct from usual care, other recognised treatment, and no-treatment controls. Although the latter are also commonly called “controls,” they do not control well for expectancy effects, do not allow for blinding, and are neither specifically designed for a given trial nor very common in efficacy or mechanistic trials. Such comparator arms would be better termed a “comparator intervention.”</p> <p>Note that we are specifically avoiding the terms “sham,” “placebo,” and “attention” control interventions for reasons specified in the text.</p>
<p>Test intervention (or tested intervention/treatment)</p>	<p>Definition: The intervention or therapy investigated by the trial.</p> <p>Synonyms: “Index” or “experimental intervention”</p>

	Sometimes “active intervention” is used as a synonym, although the distinction between active and inactive is often not clear-cut in non-pharmacological research, which is why we recommend omitting this term.
Components of interest	<p>Definition: The components of the test intervention that the researchers expect to be responsible for the efficacy of the test intervention under study.</p> <p>The components of interest are closely aligned to the research question.</p> <p>These components are sometimes called “specific” (e.g., [33]) or “characteristic” (e.g., [34]) components/factors/ingredients. However, these concepts are highly dependent on the treated condition and treatment theory.[34] Therefore, we advocate for simplified language in the context of RCTs, describing what treatment components were studied and why. This aspect is explained in further detail in Section 1.</p>
Other components not of interest in the study	<p>Definition: Components of the test intervention that the researchers do <i>not</i> intend to study.</p> <p>These components may be thought to contribute to the placebo effect and/or to other effects that are not of interest in the study.</p>
Placebo and nocebo effect	<p><i>“The placebo and nocebo effect [are changes in health outcomes that are] specifically attributable to placebo and nocebo mechanisms, [such as] the neurobiological and psychological mechanisms of expectancies [and learning]. These mechanisms are shaped, for example, by verbal instruction, or nonverbal or situational cues that affect treatment expectancies.”</i>[35] ^(p.3)</p> <p>For details on placebo and nocebo mechanisms, see, e.g., references [36–38].</p>
Placebo and nocebo response	<p>Definition: Changes in health outcomes in the control arm of an efficacy trial.</p> <p>These responses arise from the placebo or nocebo effect as well as other independent phenomena contributing to changes in outcomes in the control arm, such as regression to the mean and natural disease course.[35]</p>
(Clinical trial) Participants	<p>Definition: Persons entering a clinical trial for the purpose of receiving or participating in the trial’s interventions.</p>
Treatment provider	<p>Definition: A person providing interventions as part of a trial (can apply to both test and control interventions).</p> <p>In the case of self-management therapies, “provider” refers to the individual that introduced the trial participant to the self-management therapy. In the case of self-directed therapies using technology, a provider may refer the individual for trial participation.</p>
Researcher	<p>Definition: The individual or group designing, conducting, analysing, and reporting a trial.</p> <p>Synonym: “Investigator”</p>
Physical, psychological, and self-management (PPS) therapies	<p>Broadly, we are discussing non-surgical, non-pharmacological interventions, including all forms of manual and physical therapy, exercise and rehabilitation therapy, conversation-based and psychological therapies, mind–body, spiritual, religious, and other non-material healing practices, and educational interventions.</p>

	<p>We exclude any interventions that require the skin to be pierced surgically or with needles or the ingestion or introduction of substances (drugs, supplements, nutritional interventions). Because other opportunities and challenges for sham controls exist, we also exclude therapies based on meridian and <i>Qi</i> concepts (including traditional acupuncture and acupressure), as well as any interventions in which therapists rely on the use of devices (e.g., ultrasound, transcutaneous electrical nerve stimulation, laser, transcranial stimulation, shockwave, spinal stimulation, splinting, and braces, but not exercises using, for example, elastic bands). For the excluded therapies, we refer the reader to existing guidance.[39,28,40]</p>
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2. General considerations for the design of control interventions

2.1. Objectives of control interventions and the similarity principle of control design

Current placebo research shows that expectation and learning effects can change clinical outcomes.[41] Because control interventions aim to control for the placebo effect (apart from other confounders such as symptom regression toward the mean, spontaneous disease remission, etc.), the principal objective of control interventions is to balance the expectations of trial participants. Blinding can achieve this goal, assuming that expectations are more likely to be balanced if trial participants do not know which group they are in. Similarly, most treatment components can influence trial outcomes, either directly or through expectancy or conditioning.[42–46,25] Because these confounding effects are difficult to predict, replicating most components of the test treatment is another objective of the control intervention. These objectives translate into a design principle for control interventions in efficacy or mechanistic trials of PPS interventions:

Control interventions should replicate as many components of the investigated treatment as possible, apart from the components whose effect the trial aims to study.

In addition to balancing expectancy effects between groups, implementing this principle of similarity will reduce the risk of differential attrition of trial participants [25] and may promote acceptability to providers, thus reducing bias in multiple ways.

We recommend that test and control interventions be identical with regard to the features presented in Table 3 unless the trial aims to study a particular component of the treatment.

Table 3: Features that should be identical for test and control interventions (unless their effect is to be studied in the trial). Features are grouped into those supporting “structural equivalence,” “indistinguishability” (according to [10]), or provider-related similarity. Items marked * reached >90% agreement during the Delphi consensus process; for all other items, the agreement was 80%–90%. Items marked † were shown to be particularly influential in trial outcomes, participant blinding, or attrition in a systematic review and meta-analysis. These items are further discussed in [25]. Further supporting references for the importance of most items are also provided in the CoPPS Explanations & Elaborations supplement.

Test and control interventions should be identical for:	Explanation
<i>Items required to expose trial participants in both groups to the same amount of healthcare attention</i>	
Number of sessions *†	The number of times during which the therapy or control intervention is provided to trial participants. In self-management or exercise trials, this may refer to the number of times the participant engages in respective activities. In other trials, such as educational interventions, this may refer to the number of modules completed.
Session duration *	The duration of individual treatment sessions, modules, trainings, etc.
Session frequency *	The sequencing of treatment sessions. When sessions are scheduled according to factors such as symptom progression, participant desire, etc., the rules for sequencing should be the same in all trial arms.
Co-interventions *	Actual or permitted interventions alongside the test treatment.
Assessments and reassessments *	This includes baseline testing, follow-up assessments, and clinical assessments performed at each appointment.
Follow-up contact frequency and mode *	The number, frequency, or scheduling rules of follow-up appointments and how these are provided.
<i>Items required to balance expectations and learning effects between participants in both groups and to potentially facilitate blinding</i>	
Intervention standardisation and treatment protocol flexibility	The degree of freedom given to providers and trial participants in applying or complying with the therapy.
Fidelity monitoring *†	Ways of monitoring whether the treatment/control protocol was followed, including direct observation, recording of individual sessions, and indirect observations (e.g., asking participants/providers about treatment content).
Intervention tailoring to trial participants †	The level to which interventions are adapted to the participants' characteristics and/or preferences and the rules according to which such individualisation occurs. “Similarity” can also be achieved by highly standardised treatment protocols.
Application modes *†	The means by which treatment is delivered, e.g., manual provision, devices (e.g., exercise equipment), conversation, video, digital health delivery, etc.
Delivery formats *	Group vs. individual sessions.
Information regarding intervention efficacy *	Through providers or as part of the consent process; may be subtly communicated, e.g., through body language of non-blinded staff or providers.
Thematic content of conversations and information material	Themes may have to be different in conversation-based therapies to exclude specific treatment mechanisms, but overall discussion themes should still be similar.
Body area(s) addressed *	In individualised interventions, this refers to the criteria according to which body parts are addressed, e.g., symptomatic vs. asymptomatic.
Physical procedures performed or undergone *	Includes manual or exercise procedures, as well as sitting or lying in the case of conversation-based therapies.
Level of participant participation *	On a spectrum from completely passive to completely self-directed, this refers to both physical and cognitive participation and whether participants are similarly active or passive in both groups.

Types of procedural steps per treatment session	Such steps could be an informal conversation, followed by a case history, physical assessments, application of treatment techniques, education, re-assessment, advice, and a discharge conversation or scheduling of follow-up appointments.
Equipment or tools employed *	Equipment or tools are only acceptable for delivery of the control intervention if a comparable tool is used in the experimental group. This disqualifies the use of detuned ultrasound and other devices as control interventions in the case of PPS therapies.
Treatment-specific sensory cues †	The physical sensations involved for participants, e.g., appearance of interventions, sound levels, touch, temperature, vibration, movement, pain sensations, smells, etc.
Treatment environment *†	Locations in which treatments take place, including clinics, community settings, or participants' homes.
Personal interactions with therapy providers *	Opportunities for formal and informal interactions between trial participants and providers.
Provider characteristics (if applicable)	
Education and professional qualifications *	Apart from formal qualifications (e.g., years of training, level of education), this may include clinical focus or area of expertise.
Experience	E.g., years in practice (total and within speciality area).
Trial-specific training *	The preparation received by providers before and during a trial. Elements to consider include competencies/learning objectives of training, number of hours, content, delivery format, competency assessment, certification, etc.
Behaviour *	How providers interact with study participants (also applicable if the same providers apply both interventions), including emotional outlook, physical composure, verbal and non-verbal support, small talk, etc.
Other	
For multi-centre trials, we advise researchers to ensure homogeneity among the similarity criteria presented above.	

Side effects of a treatment can undermine blinding.[47] Whilst we do recommend that the treatment and control “feel” similar (Table 3), the replication of side effects and discomfort in a control intervention may be challenging for practical and ethical reasons. Further, the nocebo effect (i.e., negative health outcomes through expectancy and learning mechanisms) accounts for some adverse experiences[48,49], although more research is required for this field. Complying with the above recommendations would ensure that nocebo effects are balanced between the two groups.

2.2. Further considerations for trial and control intervention design

Additional comparators, such as waiting list or no-treatment groups, may elucidate the magnitude of the placebo effect. Traditional efficacy trials do not usually implement these comparators, although their inclusion can provide insights about the potential real-world effectiveness of an intervention[50] or help contextualise observed effect sizes between test and control interventions. The latter may be particularly pertinent in the field of PPS: In contrast to pill-based placebos in drug trials, most control interventions in PPS trials will not be fully “inert.” Moreover, as discussed below, researchers may not wish or be able to omit all supposedly active treatment components in the control intervention. Thus, it is unclear whether effect sizes that are comparable to drug trials can be expected. This, however, does not negate the need for well-informed power calculations

(e.g., informed by pilot testing or studies with comparable control interventions and considering the clinical meaningfulness of effects). Three-armed designs may further provide an opportunity for the assessment of multiple treatment mechanisms (including different delivery modes or dosages). However, decisions for such designs depend on feasibility and the research questions under investigation.

Similarly, a trial's hypothesis will dictate the choice of outcome measures. We conclude that neither patient-reported nor more "objective" measures are more desirable in the general context of control interventions. This decision depends primarily on the trial's objectives. Furthermore, the evidence regarding their differential susceptibility to placebo effects is inconclusive.[51] If available and appropriate, both patient-reported and more objective outcome measures can be used.[52,53]

2.3. Ethical considerations

One must consider the ethics of trials with a specifically designed control intervention in each case. Such trials are generally considered ethical when no proven treatment exists and when high-quality evidence of efficacy is lacking for the tested intervention. This includes situations in which the studied therapy is already commonly used in clinical practice [54,55] or when an established treatment is available as alternative comparator. Researchers ought to consider ethical concerns from the perspective of trial participants (see Section 3.5.).

3. Control intervention development and testing

3.1. Conceptual development

In designing a new control intervention, one should clearly define the objectives of the control intervention (see Section 2.1.).

The development of a control intervention begins as a conceptual process. First, researchers should define the physiological, cognitive, and/or behavioural mechanisms through which the tested intervention is hypothesised or known to exert its effects (also see the 'programme theory' section in the 2021 Medical Research Council guidance for complex interventions [9]). Then, they should describe which components (Table 3) of the test treatment are expected to produce clinical effects via these mechanisms. At the same time, researchers must consider all components of the test treatment and its context with regard to their potential to elicit placebo/nocebo effects. We recommend a literature review of comparable control interventions and available blinding methods to guide intervention development. Finally, the control intervention should be designed to replicate all components whilst omitting the mechanisms of the experimental treatment. As a "safety check," researchers should consider mechanisms by which the control intervention could produce unanticipated therapeutic benefits and whether these overlap with hypothesised test treatment mechanisms. In other words, the control intervention ought to be as inert as possible for the studied mechanisms.

3.2. Practical development and validation

The development of any control intervention should involve specific feasibility testing or a validation phase, either externally or as part of the trial. Previous validation of a control intervention should not replace the feasibility pre-testing of specific trial procedures or the evaluation of blinding effectiveness in each trial. When a previously validated control is adapted to a new trial intervention, repeated validation testing is required.

In validating a developed control intervention, researchers should ensure that the following quality criteria are met:

- The control intervention must be credible as a treatment (believability of the control as an intervention that will provide benefit).[56,57]
- If blinding is an objective, the control should successfully blind participants to group allocation (similar proportions of participants in both groups believe they have received the test or control treatment or do not know).[58]
- The control intervention should elicit a similar expectation of benefit as the test intervention.[56,59]

To reduce the risk of attrition and unblinding, researchers should consider how engaging and acceptable the control intervention is for trial participants and providers. Ideally, matching the components in Table 3 will produce similarly engaging interventions. However, important intervention components may be removed, and one must consider whether this removal will make the control less engaging. Early consultation of potential trial participants and providers may be helpful to enhance control intervention acceptability (see Section 3.5.).

Researchers should also consider the risk for group contamination, including information exchange between participants in different trial groups and the associated risk of unblinding. Group contamination may occur, for example, when study participants of both groups attend the same clinic, see the same group of providers, or are recruited from the same peer group. If identified, these risks of group contamination should be mitigated.

Explanations to trial participants regarding the interventions should be matched for plausibility, development of expectancies, and the need for adherence. Furthermore, written and verbal information should be presented in a manner consistent with authentic delivery methods. This matching should also be applied when obtaining informed consent within the (control) treatment session after explanations about procedures and possible risks and benefits.

3.3. Provider training: protocol fidelity, blinding, and equipoise

Participant–provider interactions should be standardised to avoid uncontrolled wording, behaviour, treatment provision, and conditioning. We encourage specific provider training that clearly delineates what is in and out of scope for control intervention delivery, so that no off-limit advice or education is provided in the control arm. Providers should receive a clear structure or protocol with operational definitions that guide control intervention encounters, supported by training. The use of suggested language may be useful when conversations cannot be (semi-) scripted. The use of video recordings to review practice consultations prior to a trial and fidelity monitoring of conversations and interactions during the trial may also be useful. During trial

preparations, staff (therapists and others) should receive training on the importance of maintaining blinding and the need to reduce unblinding risks for any party.

Provider blinding is another challenge in PPS trials. Provider expectations can influence trial results through many mechanisms, including verbal and non-verbal interactions with trial participants and deviations from trial procedures.[60,61] As such, differential provider expectations may pose a threat to a trial’s internal validity,[62] although this aspect is rarely discussed in trial reports.[17] Because it is usually impossible to conceal from providers which intervention they deliver, one must instead consider provider equipoise and allegiance. Here, equipoise means a comparable belief in the usefulness of intervention and control, and allegiance refers to the professional or personal commitment to a therapeutic modality.[63] Whilst completely balancing these factors may be unrealistic, trial designers should consider how to promote confidence in (control) treatment delivery across providers (Box 1). Further, researchers should critically reflect on their own allegiance to and belief in the study interventions.

<p>During the development of control interventions:</p> <ul style="list-style-type: none">● Consider involving providers in the development of a control intervention.● Test the control intervention with providers, assessing for acceptability and provider expectancy. <p>As a part of provider training before a trial:</p> <ul style="list-style-type: none">● Discuss the concept of equipoise and the need to adhere to trial procedures.● Educate providers about the complex nature of the tested intervention, the replication of most of its components in the control arm, and the potential benefit to participants through the placebo effect.● Discuss similarity between conditions and the many remaining components of the control (many of which they will recognise as important parts of their everyday care provision).● If required, remind providers of the ethical justifications of control interventions in clinical research and the purpose of RCTs. <p>During a trial:</p> <ul style="list-style-type: none">● When possible, standardise patient–provider interactions (e.g., using a script detailing all procedures and communications).● Evaluate provider expectancy regularly.● Monitor fidelity to intervention protocols and conversation scripts.

Box 1: Possible steps for trial designers to enhance provider confidence in (control) intervention delivery and compliance with trial procedures. These considerations can be applied to any non-blinded staff with trial participant contact.

3.4. Blinding of other parties

The blinding of outcome assessors is essential, and blinding of other involved staff should be done along with adequate allocation concealment.[64] To avoid performance and confirmation bias, treatment providers must not act as outcome assessors if they are not blinded. Statistical analyses must be blinded.[65] Since this can be difficult, pre-registration of a detailed statistical analysis plan is another important method for minimising bias during data analysis.[66,67]

3.5. Patient involvement and patient communication

Discussing the draft guidelines with people living with pain highlighted several potential enablers and barriers for trial participation and for the successful conduct of an efficacy trial of PPS interventions (see table in E&E supplement; for more details, see Supplement 2). Consequently, the expected benefit of involving potential participants in the development of a control intervention and planning of a trial is large. Enablers and barriers can be further explored through stakeholder involvement, which must be geared towards the target clinical population and therapeutic modality. Such stakeholder involvement can also be used to optimise communication with trial participants prior to, during, and after a trial. Examples include wording around the control intervention and education about its purpose.

4. Conducting a controlled trial

4.1. Fidelity monitoring and participant adherence

As described in Box 1, researchers should monitor the fidelity of providers to intervention protocols and/or conversation scripts during a trial, and participants' adherence to and compliance with interventions. These steps are particularly important for trials with prolonged treatment periods, unsupervised self-management components, or complex intervention procedures.

4.2. Measuring participant expectation and blinding effectiveness

Due to the potential implications of expectations for trial outcomes, researchers should evaluate participant expectations of benefit at baseline and after participants have started interventions.[68–70,48] Nonetheless, the influence of expectancies on trial outcomes requires further study, and better methods are needed to adequately assess these influences.[71]

Although related to participant expectation, blinding effectiveness should be assessed separately because it is a more tangible concept and an important objective of covert control interventions. To assess blinding effectiveness, researchers can ask participants to guess their group allocation. The high importance of successful blinding for most controlled trials requires blinding to be assessed at least once in any trial.

4.3. Attrition

Throughout the trial, researchers should document reasons for participants' withdrawal from the study (e.g., adverse events, lack of benefit, symptom improvement, unblinding, and others),[72,73] while recognising that participants have no duty to disclose reasons or may not disclose the true cause. However, researchers should aim to determine whether differential attrition is linked to unblinding or other aspects of the control intervention, such as a lack of credibility or acceptability that could push participants to seek care elsewhere.

5. Reporting a controlled trial

General reporting guidelines for non-pharmacological clinical trials are available, including Consolidated Standards Of Reporting Trials (CONSORT) extensions.[30,74] For reporting “placebo” or “sham” controls, a specific guide and reporting checklist exist (TIDieR-Placebo).[32] TIDieR-Placebo provides a good basis for improved reporting of control interventions, but not for their design, nor is TIDieR-Placebo specific to non-pharmacological interventions. We recommend compliance with TIDieR-Placebo. However, additional detail is required, particularly for how test and control interventions differ with regards to the features presented in Table 3.

Based on our consensus process, we recommend reporting of all items from TIDieR-Placebo [32] and seven additional items. These reporting items are explained in the supplementary E&E document.

We provide a TIDieR-Placebo/CoPPS hybrid reporting checklist to specifically improve reporting of control interventions in PPS trials, integrating our recommendations into TIDieR-Placebo (Table 4; also provided as editable checklist in the online “toolbox” supplement). Notably, this checklist is for the *reporting* of control interventions only and not to be confused with our CoPPS Checklist of essential items for control intervention development and conduct (see Table 1 and supplement). We recommend that both checklists are submitted and published alongside relevant trial manuscripts.

Table 4: TIDieR-Placebo/CoPPS reporting checklist: The Template for Intervention Description and Replication (TIDieR-Placebo) checklist was modified by adding reporting items from the Recommendations for the Development, Implementation, and Reporting of Control Interventions in Efficacy Trials of Physical, Psychological, and Self-Management Therapies (CoPPS) Statement. Added CoPPS items are illustrated in italics. In the column titled ‘where located’, trial authors should indicate where the respective information is reported in their publication or supplementary material.

Item	Where located			Where located	
	Primary paper (page or appendix number)	Other (details)		Primary paper (page or appendix number)	Other (details)
Active intervention			Placebo/sham intervention		
<i>0 Processes of sham intervention development</i>					
			<i>Sources and processes that informed the development of the control intervention.</i>		
1 Brief Name					
Provide the name or a phrase that describes the intervention			Provide the name or a phrase that describes the placebo/sham intervention		
2 Why					
Describe any rationale, theory, or goal of the elements essential to the intervention			Describe any rationale, theory, or goal of the elements essential to the placebo/sham intervention*		

			<i>Theoretical considerations underlying the control intervention (including explicit mechanistic rationales and objectives of the control intervention)</i>		
3 What (materials)					
			<i>A highly detailed description of the content of the control intervention (covering all components listed in table 2 of the CoPPS publication and including resemblance or differences to the test intervention)</i>		
Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as online appendix, URL)			Describe any physical or informational materials used in the placebo/sham intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (such as an online appendix, URL)		
4 What (procedures)					
Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities			Describe each of the procedures, activities, and/or processes used in the placebo/sham intervention, including any enabling or support activities		
5 Who provided					
For each category of intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given <i>Should also include a description of provider behaviour, verbal and non-verbal communication, and issues of equipoise as detailed in the text of the CoPPS Statement and its Explanations & Elaborations document; as well as means to control these provider-related factors.</i>			For each category of placebo/sham intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given <i>Should also include a description of provider behaviour, verbal and non-verbal communication, and issues of equipoise as detailed in the text of the CoPPS Statement and its Explanations & Elaborations document; as well as means to control</i>		

			<i>these provider-related factors.</i>		
<i>Additional provider-related information</i> <i>Reporting should further include how issues of equipoise and provider expectancy were addressed; and if and how provider behaviour and verbal and non-verbal communication were controlled in each group. If different sets of providers were employed to deliver test and control interventions, this needs to be reported along with differences in their characteristics.</i>			<i>Additional provider-related information</i> <i>Reporting should further include how issues of equipoise and provider expectancy were addressed; and if and how provider behaviour and verbal and non-verbal communication were controlled in each group. If different sets of providers were employed to deliver test and control interventions, this needs to be reported along with differences in their characteristics.</i>		
6 How					
Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group			Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the placebo/sham intervention and whether it was provided individually or in a group		
7 Where					
Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features			Describe the type(s) of locations(s) and settings where the placebo/sham intervention occurred, including any necessary infrastructure or relevant features		
8 When and how much					
Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose			Describe the number of times the placebo/sham intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose. If relevant, include the duration of the pre-, and post-randomisation consultations		
9 Tailoring					
If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how			If the placebo/sham intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how		

10 Modifications					
If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)			If the placebo/sham intervention was modified during the course of the study, describe the changes (what, why, when, and how)		
11 How well: planned					
Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them			Planned: If placebo/sham intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them		
12 How well: actual					
Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned			Actual: If placebo/sham intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned		
			<i>Whether any reasons for loss to follow-up (participant attrition) or non-adherence during the trial were related to the control intervention.</i>		
13 Measuring the success of blinding					
Was blinding measured, and if so: how, and what were the results of such measurement? <i>Blinding should always be assessed if it was an objective of the control intervention, and results should be reported as summary statistics per group, allowing independent calculation of blinding indices.</i>			<i>Blinding should always be assessed if it was an objective of the control intervention, and results should be reported as summary statistics per group, allowing independent calculation of blinding indices.</i>		
14 Assessment of participant expectation					
<i>Report the method of assessment, timepoints, and results as summary statistics per group.</i>			<i>Report the method of assessment, timepoints, and results as summary statistics per group.</i>		

This table was reproduced in accordance with the Creative Commons Attribution license (CC BY), and is based on the original TIDieR-Placebo checklist as published in: Howick J, Webster RK, Rees JL, *et al.* TIDieR-Placebo: A guide and checklist for reporting placebo and sham controls. *PLOS Medicine* 2020;**17**:e1003294. doi:[10.1371/journal.pmed.1003294](https://doi.org/10.1371/journal.pmed.1003294)

6. Interpreting efficacy and mechanistic RCTs of PPS interventions

In complex interventions, treatment components may not always interact in an additive manner, but may interact in unpredictable ways.[75,9] Complexity also arises from interactions with the context in which complex interventions are implemented.[9] For example, a good therapeutic relationship may reinforce the effects of a particular treatment component, for instance by increasing treatment adherence and motivation, but the extent of such an effect is difficult to predict [76] and may vary with context. In the control intervention, the composition of the components is altered, which may lead to different interactions. Mediation and moderation analyses may facilitate the interpretation of these effects on trial participants,[77–79] as well as existing mechanistic studies [80] and balanced placebo designs.[81] For cases in which multiple components are removed from the control, the mechanistic interpretation becomes even more complex. Importantly, when control interventions are designed according to the principles presented here, studies will reflect the efficacy of the tested component, and only this component, and the involved treatment mechanisms. In contrast to drugs, complex interventions rarely act on a single mechanism. Thus, results usually cannot directly answer questions of real-world effectiveness or reflect (lack of) efficacy of the intervention as a whole.[82]

Similarly, choices made in the design of the control intervention determine the mechanism studied. There is always the possibility that the supposed mechanism of effect was wrongly conceptualised. Thus, conceptual clarity about and transparent reporting of control interventions are paramount to facilitate interpretation and evidence synthesis.

Finally, effect sizes have to be interpreted carefully in efficacy trials with high-similarity control interventions.[83] Although such control interventions are important for obtaining a mechanistic understanding of an intervention and for bias control, trials that control for all but one component of a complex intervention cannot be expected to show effect sizes comparable to those of drug trials, where a single pharmacological ingredient may primarily account for the benefit over placebo. However, more research on the directionality, extent, and variability of effect estimates in non-pharmacological efficacy trials is required, also accounting for the unclear influence of blinding.[84–87] Effect sizes of efficacy trials may also not reflect the effects that can be obtained in real-world practice or the benefits over structurally different “usual care.” However, positive signs from an efficacy trial with a well-designed control intervention should increase end-users’ confidence in an intervention under real-world conditions, even if effect sizes in the efficacy trial are small. Hence, well-designed pragmatic trials or additional comparator arms are useful for further elucidating questions of comparative and real-world effectiveness.

Limitations

We have presented a consensus statement for the development, implementation, and reporting of control interventions in efficacy and mechanistic trials of PPS interventions. A limitation of this statement is that, despite targeted efforts to recruit individuals from low- or medium-income countries, the author group included no experts from these areas (Supplement 1a). Additionally, few individuals were recruited from scientific communities in which English is not the dominant language. This may impact the generalizability of our recommendations to other cultures, healthcare systems, or languages. Second, the consensus process originally focused on pain as

primary outcome and primarily involved individuals with expertise in pain research. However, due to our focus on best-practice principles and interventions rather than conditions, it became clear during the process that this guideline is broadly applicable, especially to trials exploring complex, persistent, or recurring health problems and symptoms that are amenable to expectancy effects. Examples include the mental health field, but as described above, the CoPPS Statement must be considered in the context of the given patient population and research question.

Concluding remarks

The successful development and implementation of a control intervention adds considerable expense to a clinical trial and can be burdensome to trial stakeholders. Nonetheless, excessive trade-offs between control design and research burden can undermine the interpretability of trial results. Without trust in the quality and success of the control, the conclusions that can be drawn from a trial are weakened. To support end-users, we call for researchers and journal editors to improve reporting practices, including full, transparent reporting of control intervention content and blinding effectiveness.

In the management of individuals with chronic conditions, guidelines call for changes in psychosocial and lifestyle factors; thus, research into non-pharmacological non-invasive alternative treatments abounds. Created for a field with particular challenges for blinding and control intervention design, this guidance provides a robust framework for high-quality efficacy and mechanistic trials of PPS interventions. The guidance acknowledges that this field is distinct from drug research, requiring a contextualised interpretation of trial results and proposing specific solutions for trial designers. Thanks to a rigorous consensus process with experts in placebo research and patient partners, trial designers now have access to unifying principles of best-practice control intervention development and implementation during a trial, amenable to specific research scenarios and potentially generalisable to other non-pharmacological research fields.

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Data sharing

Data from the Delphi study and patient interviews are available in supplements. Anonymised transcripts of consensus meetings and patient interviews are available from the corresponding author upon request.

Author contributions

DHS, LV, JV, WS, JDR, and ASCR made substantial contributions to the conception and design of the work and the analysis and interpretation of data. Further, DHS and JDR collected data as part of the Delphi process, interviews with patient partners, and facilitation of consensus workshops. All authors except DHS, LV, JV, WS, JDR, and ASCR participated in at least two Delphi rounds, and all except WS, EC, DH, JV, and MA actively participated in at least one consensus workshop. DHS drafted the manuscript, and all other authors revised it and/or re-drafted sections through three rounds of internal review and as part of consensus workshop discussions. JV had a supervisory role and guided the revision of the manuscript during the publication process. DHS is the guarantor of this work. All authors approved the final manuscript version and agreed to be accountable for all aspects of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Patient and public involvement

The involvement of patient representatives is detailed in the article and respective supplementary material. Patients or members of the public did not participate in the design of the study but contributed through specific patient-centred interviews, consensus meetings, and review of the manuscript. The published article will be disseminated through patient networks involved in the recruitment of patient representatives into this study.

Funding and sponsor role

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Dissemination plans

The methodological processes and systematic review leading up to the CoPPS Statement have been presented at international conferences. Following publication and to promote the uptake of the guideline, we will: Circulate the CoPPS Statement to relevant professional bodies (such as physiotherapy and psychotherapy associations) for dissemination amongst members, and to other stakeholders (notably funders of clinical trials). For that, we will mainly use an executive summary and the infographic included in this paper; Present the CoPPS Statement at relevant clinical trials methodology and discipline-specific conferences, on occasion applying the guideline to example trials as part of workshops; Offer training workshops and webinars to educate researchers, practitioners, and funding organisations on the importance of using control interventions in clinical trials and how to implement the recommended practices; Engage with stakeholders, including patients, advocacy groups, and industry partners, to promote the uptake of the recommendations and increase the impact of the research; Apply for addition of the CoPPS/TIDieR-Placebo hybrid reporting checklist to the EQUATOR network website (<https://www.equator-network.org/>), which will also improve visibility of the CoPPS Statement as a whole; Monitor the adoption and impact of the recommendations through follow-up surveys, reviews, and evaluations, and publish updates to the guidelines as needed.

Competing interests

All authors have completed the ICMJE uniform disclosure form at <http://www.icmje.org/disclosure-of-interest/> and declare:

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