# Explanations and Elaborations document (E&E) for the CoPPS Statement and Checklist

This E&E document is to be used in conjunction with the CoPPS Statement and Checklist when developing, conducting, or reporting a control intervention in an efficacy or mechanistic trial of a physical, psychological, or self-management intervention. The E&E document follows the same numbering as the CoPPS Statement and Checklist. Essential recommendation items are identified in boxes, explained, and illustrated with practical examples.

**Original reference of the CoPPS Statement:**

Hohenschurz-Schmidt, D.*, Vase, L., Scott, W., Annoni, M., Ajayi, O.K., Barth, J., Bennell, K., Berna, C., Bialosky, J., Braithwaite, F., Finnerup, N.B., Williams, A.C. de C., Carlino, E., Cerritelli, F., Chaibi, A., Cherkin, D., Colloca, L., Côté, P., Darnall, B.D., Evans, R., Fabre, L., Faria, V., French, S., Gerger, H., Häuser, W., Hinman, R.S., Ho, D., Janssens, T., Jensen, K., Lunde, S.J., Keefe, F., Kerns, R.D., Koechlin, H., Kongsted, A., Michener, L.A., Moerman, D.E., Musial, F., Newell, D., Nicholas, M., Palermo, T.M., Palermo, S., Peerdeman, K.J., Pogatzki-Zahn, E.M., Puhl, A.A., Roberts, L., Rossettini, G., Johnston, C., Matthiesen, S.T., Underwood, M., Vaucher, P., Vollert, J., Wartolowska, K., Weimer, K., Werner, C.P., Rice, A.S.C., Draper-Rodi, J., 2023. 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. *BMJ*.

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## Background (E&E)

### *Objectives of the CoPPS Statement*

The Recommendations for the Development, Implementation, and Reporting of Control Interventions in Efficacy and Mechanistic Trials of Physical, Psychological, and Self-Management Therapies (CoPPS Statement) are based on a specifically conducted systematic review of control methods and a consensus-finding process both with experts in placebo research or trials of physical, psychological, and self-management (PPS) interventions for pain and with people living with pain. The systematic review clearly showed that control intervention design is heterogeneous in the field [1] and that similarity levels between test and control interventions influence trial outcomes, including clinical results and blinding effectiveness.[2] The consensus-finding process led to a decision-making framework applicable to all PPS therapies, a checklist of core recommendations, and a reporting checklist. Whilst the core recommendations seek to establish a basic quality standard in the field, the surrounding decision-making framework acknowledges the practical constraints of clinical trials and the complexity of control intervention design and implementation, leaving room for innovation and creative solutions. There is no perfect control intervention in PPS trials. Instead, these recommendations provide researchers with considerations to guide their decision-making at each step of trial design, conduct, and reporting. Policymakers, clinicians, service-users, and other stakeholders may use this framework to better judge the quality and applicability of control interventions in trials of respective therapies.

### *Scope of the CoPPS Statement: Type of interventions*

The CoPPS Statement focuses on PPS interventions, entailing cognitive-behavioural approaches, exercise and rehabilitation, manual therapies, mind-body techniques such as yoga and meditation, and education. Notably, for the purpose of this guideline, the PPS umbrella does not include device-delivered therapies, where the sham control intervention often simply involves detuned devices;[3] surgery where much work on sham controls is conducted and that benefits from general anaesthesia for blinding;[4–7] and acupuncture, employing needling in non-acupuncture points or non- or low-level penetrating sham needles, resulting in a reasonable opportunity for participant blinding.[8–10] These therapies are therefore not discussed here.

### *Scope of the CoPPS Statement: Type of clinical trials*

The CoPPS Statement notes that the control interventions discussed here tend to be used in trials on the explanatory end of an explanatory-pragmatic continuum,[11,12] because they are useful to study the efficacy of a given intervention or its mechanisms of action. “Efficacy” refers to testing treatment benefits and harms under highly controlled conditions. Efficacy trials are those that focus on the standardisation and optimisation of treatment delivery to “observ[e] an intervention effect if one exists” [13] and/or on bias minimisation to increase confidence that any observed effect is due to the intervention.[14] Control interventions, as discussed in the CoPPS Statement, are an important method for reducing bias.

Further, the removal of particular treatment components of the control intervention allows one to study the effects *of these components* – and these components only (see Section 6) – and thus to hypothesise on treatment mechanisms (also known as mechanistic or explanatory research). However, research questions concerning the comparative effectiveness of a treatment may require different comparator conditions altogether, usually another recognised treatment or usual care. Many design aspects other than the choice of comparator influence how “pragmatic” a trial is and thus its relevance for real-world decision-making.[11,15–18]

Choosing the ideal comparator for a given research question is a fundamental step for any clinical trial, and there is ample literature to guide this decision.[19,20] The present guidance does not seek to reinforce the antiquated notion of randomised placebo-controlled trials as the gold standard of clinical research.[21] Instead, this guideline intends to improve the design of control interventions *once researchers have decided that a specifically designed control intervention is required for their research question*. As described above, this is usually the case in so-called efficacy and mechanistic randomised controlled trials (RCTs). According to the 2021 Medical Research Council (MRC) guidance for complex intervention development and evaluation,[22] efficacy and mechanistic trials are important to evaluate mechanisms of change and causal links between intervention components and outcomes. The guidance emphasises, however, that in a pluralistic research framework, perspectives other than that of 'efficacy' are additionally required, as is the early engagement of key stakeholders, to ensure that interventions can be implemented in various contexts. For such and other research questions and how they might apply to their intervention of interest, readers are referred to the MRC publication.[22] In providing a unifying best-practice framework for efficacy and mechanistic trials in PPS research, the CoPPS statement promotes better-quality efficacy research, allowing for more robust conclusions about treatment mechanisms and mediators of treatment effects than can be achieved in trials with exclusively active comparators or low-quality controls. These insights can then be used to inform other research questions, for example those that are implementation-focused.[22]

Importantly, the control interventions discussed here are specifically designed for efficacy or mechanistic research and are distinct from the comparator treatments in comparative effectiveness trials, which test treatments against another recognised intervention or usual care.[7] Finally, specifically designed control conditions can be used to study the placebo effect itself. This may require further considerations that are beyond the scope of this guideline.

## 1. Terminology and communication (E&E)

The CoPPS Statement proposes a simplification of language, avoiding potentially ambiguous or negatively connotated terms such as "placebo" or "sham control." Understanding is further hindered by related notions such as "contextual," "specific," and "non-specific" ingredients (or similar).[34]

This change in terminology reflects the experts' attempt to acknowledge fundamental differences between trials of drugs and non-pharmacological interventions. First, mechanisms of PPS therapies are often unclear, or there may be multiple mechanisms interacting in complex ways, making their isolation and relative assessment by using a control intervention difficult.[2–4] Second, when designed for complex interventions, control interventions are unlikely to be truly "inert."[5] Indeed, what may be a control intervention component in one trial (e.g., touch in a spinal manipulation trial or education in a cognitive-behavioural intervention trial) may well be the investigational treatment in another (e.g., touch in a trial of therapeutic touch or education in a trial of pain neuroscience education).[4] Third, many PPS therapies rely on active participation of patients and interaction with providers. Consequently, provider blinding is often impossible and participant blinding difficult in such trials[6], thereby increasing the risk of the trial outcomes being influenced by expectation biases. When trying to apply quality standards for placebo-controlled drug trials to trials of non-pharmacological interventions, such differences are typically not considered. In fact, these differences mean that the term "placebo" can be confusing and ambiguous in non-pharmacological trials. Instead, the term "sham" is commonly used, but this term has negative connotations of deceit and falseness and creates problems of translation into other languages. Throughout the CoPPS guideline, we therefore refer to "control interventions" rather than "placebo," emphasising the above fundamental differences between drug and non-drug interventions. For scientific communication, this approach still differentiates control interventions of efficacy trials (defined as per above) and comparator treatments in comparative effectiveness trials. The latter are not specifically designed to study the effects

or mechanisms of particular components of the test intervention, but rather to compare one treatment against another commonly available treatment option.

## 2. General considerations for the design of control interventions

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

**Essential recommendation item(s)**

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

*(CoPPS Statement and Checklist reference: 2.1)*

One of the main criticisms of complex intervention trials is the difficulty of blinding trial participants to group allocation. This guidance aims to overcome these challenges, accepting that perfect blinding may not always be possible, but postulating that comparable expectations and context-dependent effects between groups can be obtained by making the intervention and control as similar as possible in every aspect but the component(s) to be studied. Other considerations in this guideline, including communication with trial participants, have the same goal of balancing expectations. An important additional effect of this 'similarity principle' is the reduction of bias by other means, such as increasing acceptability of the control intervention for providers and participants. The 'similarity principle' is thus closely aligned with the ambition of efficacy trials to minimise bias.

A wide body of theoretical and empirical research suggests that social and environmental factors influence the magnitude of placebo effects,[8,23–30] specific aspects of which are summarised in Table 3 of the CoPPS Statement. For a detailed discussion on why some similarity features may be more important than others (as indicated in Table 3 of the CoPPS Statement), readers are referred to an accompanying meta-analysis that tested the association between (dis)similarity and trial outcomes.[2]

**Example:** Alkhawajah & Alshami [31] provide a clear description of the similarity between their investigational and control interventions and identify the treatment component omitted from the control intervention. The similarity of providers and treatment environments, however, can only be inferred from their report:

"*In the treatment group, the therapist applied the glide force on the tibia with the knee in mid-range. Then this force was maintained while the patient was flexing and extending the knee to full range. Overpressure was performed at the end range. The MWM [mobilization with movement] treatment technique was repeated 10 times for three sets […]. In the sham group, the patients were handled similarly to those in the treatment group, but [the therapist] did not [perform] the [directional] glide. [Instead], the therapist's hands were lightly touching the knee skin without pressure, one hand on the tibia and one on the femur. Active knee flexion and extension movements, however, were performed 10 times for three sets*."

### *2.2. Further considerations for trial and control intervention design*

All relevant explanations or elaborations regarding the use of additional comparators or the choice of outcome measures are provided in the main CoPPS Statement.

**Example:** Chaibi et al. [32] conducted a three-armed trial, clearly identifying the objectives pursued with each study condition:

"*The second objective was to assess the efficacy of CSMT [chiropractic spinal manipulative therapy] versus sham manipulation (placebo) and CSMT versus controls, i.e. participants who continued their usual pharmacological management*."

### *2.3. Ethical considerations*

**Essential recommendation item(s)**

- Consider ethical arguments for and against performing an efficacy or mechanistic trial with a control intervention, including from the perspective of a trial participant.

*(CoPPS Statement and Checklist reference: 2.3)*

Apart from considering whether a trial with a specifically designed control intervention is ethical, the expected research benefits afforded by the trial must outweigh the risks of being assigned to the control group.[33,34]

Further ethical concerns from a trial participant's perspective may include whether the proposed trial makes the best use of the participant's time and whether the research burden is acceptable, even when allocated to the control intervention.

The decision to deceive trial participants and other involved parties requires careful assessment of involved risks and methodological alternatives.[7,35] Deceit, in the present context, refers to misleading participants about the true aim of the study, the nature of the interventions, or the existence of a control group; it does not refer to the strategic omission of information about group allocation for blinding purposes, which is usually covered in the informed consent process. Researchers adopting deceptive trial designs require a waiver of standard informed consent from a competent ethics committee, as deceit is incompatible with valid informed consent.[36]

Finally, misconceptions around the purpose of clinical trials, the control interventions, and the nature of the placebo effect should be addressed during the informed consent process.[37,34] The findings from our patient interviews support such communication (presented below, Section 3.5).

**Example 1:** Ethical considerations pertain to many aspects of trial design and are rarely reported comprehensively,[38,39] particularly for aspects concerning the control intervention.[1] Albeit not a perfect example, Walker et al. [40] touch on the ethics of communication during the informed consent process and on the justification for conducting a controlled efficacy trial:

"*The information letter provided to potential participants stated that the study will compare one type of chiropractic treatment that has unknown benefits for back pain with another type of chiropractic treatment that is not thought to be beneficial for back pain*."

**Example 2:** In an early validation study of a sham spinal manipulation procedure from 2005, Vernon et al. [41] outline the ethical argument for conducting trials with such control interventions in their field:

"*The ethical justification for the use of a placebo group in clinical trials lies in the concept of "clinical equipoise,"[…] which, when justified, permits investigators to, as Freedman […] states, "have no 'treatment preference' throughout the course of the trial." The arguments presented above on the need for placebo-controlled research in spinal manipulation, as well as the lack of such trials in key clinical areas,*

*establish the general basis for clinical equipoise in this field of work. Once this is accepted, the need for a valid placebo maneuver becomes paramount and the issues that distinguish this type of placebo from the kind of inert pill used in drug trials become obvious*."

## 3. Control intervention development and testing

### *3.1. Conceptual development*

**Essential recommendation item(s)**

- Clearly define the objectives of the control intervention in the context of the research question at hand.
- Perform a literature review of comparable control interventions and their available blinding data.
- Define the mechanism(s) of interest of the test intervention.
- Specify the components of the test intervention thought to act on the above mechanism(s).
- Ensure that the control intervention is inert for the studied mechanism(s) and does not include the component(s) of interest.

*(CoPPS Statement and Checklist reference: 3.1)*

The above recommendations provide a step-by-step guide for the conceptual development of a control intervention in the context of a specific research question and trial. However, they hinge on a theoretical understanding of the treatment mechanisms to be tested. In the common scenario where there is no clear understanding of the neurobiological treatment mechanism(s), researchers still require a hypothesis that can be tested with a controlled trial, intending to add to the mechanistic understanding in their field. Such hypotheses can arise from preclinical or other experimental work or from relevant theory and should be subjected to stakeholder scrutiny. Prevalent theories within a profession can be a starting point for control development when neurobiological mechanisms are unknown; however, one must recognise that intervention theory necessarily simplifies clinical reality, where intervention components are rarely independent from one another.[42] Simply replicating existing theory thus may not always contribute to a greater understanding of mechanisms.[43]

Most PPS interventions are complex in nature, containing many potentially therapeutic components.[22,44,45] It may be desirable to study the effects of several components in a single trial, in which case the above process is applied multiple times to design a control intervention that omits multiple test treatment components. In this instance, however, outcomes may become even more difficult to interpret mechanistically. Moreover, test and control interventions become successively less similar, with potential implications for blinding and placebo effects, and thus risk of bias. Iterative research approaches or multiple control intervention arms appear useful but may be impractical and costly. Where feasible, however, trial iterations or multiple control arms allow for the testing of different intervention aspects, such as mechanisms, dosages, or delivery modes.

**Example 1:** Gonzáles et al. [46] specify the objectives of the control intervention:

"*A suitable sham NM [neurodynamic mobilization] comparator will allow investigators to blind patients with LBP [low back pain] and reduce bias by limiting the confounding effects of expectations from the participants* […]."

They identify the hypothesised mechanism of action:

"*Neural mobilization (NM) techniques are a form of manual therapy, which promote movement between nerves and their surrounding structures through positioning and movement of joints to facilitate either neural tensioning or sliding (Butler, DS.; Jones, 1991; Coppieters and Butler, 2008; Shacklock, 2005). Neurodynamic techniques are thought to promote healthy nerve function by reducing oedema and changing intraneural pressure,* […]."

They also explain how this mechanism is avoided by the control intervention:

"*The therapist passively moved the patient's leg up to 30◦ of hip flexion* […]. *This technique was designed in order to limit sciatic nerve stress,* […]."

Finally, Gonzáles' work draws on a previously validated control intervention for a different body part:

"*A sham NM technique has been previously validated in the treatment of carpal tunnel syndrome (Bialosky et al., 2009), […]. It was successful in blinding participants to their assigned intervention and produced a similar expectation for treatment success compared to the real NM.*"

**Example 2:** Evaluating a novel control intervention, Davies et al. [47] examined whether the control intervention affected the hypothesised target mechanism of the investigational treatment:

"*The sham mindfulness […] did not influence mindfulness-related processes. In contrast, mindfulness increased "observing" relative to no treatment but not sham*."

### *3.2. Practical development and validation*

**Essential recommendation item(s)**

- Test the control intervention in a feasibility or validation step, ensuring that certain quality criteria are met (see CoPPS Statement).
- Consider and mitigate, if required, the risk of group contamination.

*(CoPPS Statement and Checklist reference: 3.2)*

All relevant explanations or elaborations for this topic are provided in the main CoPPS Statement.

**Example 1:** In their validation study, Chaibi et al. [48] describe how they measured blinding effectiveness and treatment credibility. Participants' expectations of benefit were not measured.

"*After each treatment session, the participants completed the de-blinding questionnaire administered exclusively by a blinded external trained independent party with no involvement from the clinical investigator, i.e., providing a dichotomous "yes" or "no" answer as to whether active treatment was received. This response was followed by a second question regarding how certain they were that active treatment was received on a 0–10 numeric rating scale (NRS), where 0 represented absolutely uncertain and 10 represented absolutely certainty* […]."

**Example 2:** In a feasibility study, Stanton et al. [49] explored control-related aspects through qualitative methods, from both participants' and providers' perspectives. They also studied intervention adherence and retention to follow-up.

"*Participants' and treating clinicians' perspectives on the acceptability of the clinical interventions were gathered. Intervention format, content acceptability and usefulness, as well as perceived credibility were assessed using a purpose-designed Participant Experience Questionnaire (PEQ; 5-point Likert scale ranging from "strongly agree" to "strongly disagree"), short-answer questions at 4, 8, and 26 weeks, and audio-recorded telephone interviews at 4 and 8 weeks* […]. *Control participant's PEQ credibility ratings were used to assess sham ultrasound credibility. Short-answer questions and interviews explored what participants liked the most/least about the treatment, and their suggestions for the content and format of the sessions. Treating clinicians judged the perceived acceptability of the intervention to the participant at weeks 4 and 8 (Do you think the participant found this to be an acceptable intervention? Yes/No), and, at trial conclusion, completed 4 short-answer questions, supplemented by verbal interview, about their experience delivering the treatment and on content and format* […]."

**Example 3:** Although not an efficacy trial, a process evaluation of the Falls in Care Homes (FinCH) trial illustrates a rigorous approach to the reduction of contamination risk.[50] The authors first identified potential mechanisms for the introduction of contamination bias in their trial setting, and then implemented specific mitigation strategies as part of their trial design. Such strategies included open communication about contamination risks with clinical teams and management, and the continuous screening for conflicting initiatives for fall prevention that might inadvertently influence the control group. The trial's cluster design was likely also beneficial. Also see experiences from Health, Exercise and Nutrition for the Really Young (HENRY) feasibility study, where trial providers were identified as a main source of possible contamination.[51]

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

**Essential recommendation item(s)**

- Providers should be specifically trained to deliver the control intervention (if applicable).
- Staff (not just treatment providers) must be educated to recognise the importance of maintaining effective blinding (if applicable).

*(CoPPS Statement and Checklist reference: 3.3)*

Provider characteristics have the potential to influence trial outcomes.[52,53,30] Similarly, outcomes may be influenced by differences in protocolisation of (control) interventions, provider training and supervision, and fidelity monitoring, as shown in psychotherapy trials for depression.[54] For this reason, the CoPPS Statement recommends matching of certain provider characteristics between trial arms (Section 2.1), standardisation of participant–provider interactions, training and education of providers and other staff (this section, 3.3), and fidelity monitoring (Section 4.1).

In addition, providers' expectations and sentiments towards the tested and control interventions are important considerations.[55,56] Because provider blinding is often impossible in PPS trials, provider expectations should be balanced as much as possible between trial groups. In some cases, this is best achieved by employing the same set of providers for both groups; there is currently no evidence that this 'crossing' of providers between groups introduces bias [54]. In other scenarios this may be impossible for

logistical reasons or when a provider's allegiance to the test intervention or feelings of deceit regarding the control intervention disrupt their ability to deliver the control treatment with the same confidence. In these cases, providers may be allocated according to their expectations or randomised to treatment and control, thus balancing some of the expectancy effects. However, this approach is limited in its ability to account for differences in provider personality and experience, and thus additional training, standardisation, and fidelity monitoring may be required. Recommendations to enhance similarity between test and control intervention providers are presented in Table 3 of the CoPPS Statement, and include consideration of professional qualifications, experience, trial-specific training, and behaviour. Measuring provider expectations of benefit from the control versus the test intervention [57,58] is important to assess the risk of this factor influencing the trial, even more so when different sets of providers are employed.

Section 3.3 of the CoPPS Statement also presents a list of possible steps to enhance provider confidence during the delivery of (control) interventions and compliance with trial procedures.

**Example 1:** In their trial report, Nguyen et al. [59] discuss how they accounted for unblinded providers. They also state that:

"*[All providers] received a 2-day training according to international standards to deliver both standard and sham OMT [osteopathic manipulative treatment]*."

This provider training is detailed in the report's supplement:

"*Presentation of the study as well as the basic methodological principles for assessment of a complex intervention, presentation and detailed description of the clinical procedures for the experimental and sham groups, […] and distribution of the DVD showing the techniques*."

They implemented additional measures to limit bias introduced by providers:

"*Osteopathic practitioners were not allowed to have contact with participants outside of the sessions*."

Finally, Nguyen et al. scripted parts of the providers' communication and assessed fidelity retrospectively:

"*To ascertain that the osteopathic practitioners' speech was consistent in both groups, OMT sessions were audio recorded. Two sociologists […] qualitatively assessed 60 randomly selected audio records (30 from each group). They used 23 items to assess the duration of the sessions, the respect of the recommendations for verbal behavior, the content of the speech, and the verbal attitude*."

**Example 2:** Sullivan et al. [60] describe their approach to therapist equipoise in the Treatment of Meniscal Tear in Osteoarthritis (TeMPO) trial, a four-arm RCT of physical therapy and home exercise programmes, also including a 'placebo' arm:

"*Early in the trial design process, we assessed equipoise among interested therapists who might deliver the interventions. Investigators clarified that therapists who were uncomfortable with providing placebo interventions should not participate in the trial. The same therapists deliver both the placebo and 'true' PT [physical therapy] regimens to eliminate bias in treatment effect by the personal qualities of individual therapists. Once therapists were selected, discussions were held with all therapists to determine the specific components of the placebo and true PT interventions. […] During trial operation, regular therapist check-ins are held each month to discuss any concerns in the PT treatment arms*."

### *3.4. Blinding of other parties*

**Essential recommendation item(s)**

- Outcome assessors must be blinded.
- The roles of treatment providers and outcome assessors must be separated if providers cannot be blinded.
- Statistical analyses must be blinded.

*(CoPPS Statement and Checklist reference: 3.4)*

Additional valuable suggestions to optimise assessor blinding are provided by Mataix-Cols & Anderson.[61]

While blinding of outcome assessors is paramount, blinding of other staff may not always be possible or needed. If administrative and other staff cannot be blinded, trialists are referred to Section 3.3 for a list of measures to mitigate any potential risk.

Also note that the Consolidated Standards of Reporting Trials (CONSORT) Statement requires the reporting of the blinding status of involved parties and the blinding methods employed. In addition, the CONSORT extension for randomised trials of nonpharmacologic treatments asks for a description of any attempts to limit bias if blinding was not possible.[62]

**Example:** Nicholas et al. [63] report the separation of treatment provider and outcome assessor roles, thus facilitating assessor blinding:

"*The pre-treatment, posttreatment, and 1-month follow-up assessments were conducted by an external research assistant who was blinded to the nature of the treatment being received by the participants*."

### *3.5. Patient involvement and patient communication*

There was no consensus during the CoPPS Delphi study on whether control intervention development should involve consulting with patients, practitioners, and/or public involvement groups. Likely, practical and context-specific concerns prevented such consensus. Stakeholder involvement for control intervention development is also rarely reported in published trials or protocols.[1]

However, experts agreed during the subsequent discussions that the expected benefit of involving potential participants in the development of a control intervention and planning of a trial is large, but that such stakeholder involvement must be geared towards the target clinical population and therapeutic modality (a notion which is aligned with current MRC guidance for complex intervention development and evaluation[22]). This recommendation was informed by the CoPPS-specific patient involvement exercise, which demonstrated the potential value of a lived-experience perspective. The below table presents these findings and may serve as inspiration for researchers' own stakeholder involvement (E&E Table 1). Methodological details, interview scripts, sample characteristics, and detailed results are provided in Supplement 2 of the CoPPS Statement.

**Table 1 (E&E): The lived-experience perspective on potential barriers and enablers for participation in efficacy trials of PPS interventions with a specifically designed control intervention.** The table content is based on interviews with eight people with various pain-related experiences, during which hypothetical trial scenarios were discussed.

| Theme and explanation | Potential incorporation in trial development and implementation |
|---|---|
| *Barriers* | |
| **Fear of adverse effects**<br><br>Some people were worried about being assigned to a "sham" or otherwise not commonly used control intervention, fearing it might aggravate their symptoms. Others were equally apprehensive about assignment to any trial arm for the same reason.<br><br>*"Could the researchers guarantee that if I was assigned to the sham group, it wouldn't make my pain worse?"* | Fear of adverse effects can be partly mitigated by involving other people with experience of the studied condition in the development (and testing) of the control intervention and communicating this involvement to potential trial participants.<br><br>Fear can also be addressed in the informed consent process, clearly communicating the purpose of the control intervention and its resemblance to the test intervention. Communicating about trial interventions should not, however, unbalance participant expectations of benefit or harm. |
| **Burden of trial participation**<br><br>People living with long-term or very disabling pain noted mainly practical concerns; for others, the time commitment of participating in a trial was seen as potentially burdensome. The possibility of receiving a "fake" treatment exacerbated this concern. | Concerns about the burden of trial participation may possibly be mitigated by patient involvement during development of the intervention. |
| **Terminology: Avoid "sham," prefer "placebo"**<br><br>"*I mean, my first thought would be… sham just sounds like fake*." | See Section 1, "Terminology and communication," of the CoPPS Statement.<br><br>Having considered both the preference of the interview participants for the term "placebo control" and the concerns of research experts regarding the lay understanding of this term, we recommend describing the control intervention not as "sham" or "placebo" but instead in relation to the test treatment. This approach will improve understanding and mitigate all parties' concerns. |
| **Lack of understanding of control interventions** | |

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|---|---|
| Understanding of the concept of control treatments was largely vague, contributing to concerns about adverse events and the burden of taking part in a trial. Explaining the concept was reassuring.<br><br>"*How would you devise a fake treatment*?" | Education about control interventions and the purpose of controlled trials can be included in the informed consent process. |
| *Enablers* | |
| **Understanding of the placebo effect**<br><br>Many participants felt that just taking part in a trial may come with benefits, often explicitly attributed to the placebo effect.<br><br>"*But I also know about the placebo effect; If you come into the trial and very much want an outcome, you might get one, either way*." | The placebo effect could be discussed during the informed consent process. Balancing of expectations should again be the aim, emphasising that both groups will experience comparable placebo effects. |
| **Understanding of trial design and control principles**<br><br>"*If I know as a participant that I'm in the placebo arm, then I still want to make sure that the placebo side is well-studied to that there's a valid comparison*." | An improved understanding of trial design and control principles may mitigate the risk of attrition in cases of unblinding or doubt, and may facilitate enrolment.<br><br>As above, education about control interventions and the purpose of controlled trials can be included in the informed consent process. |
| **"Greater good" – Understanding of research purpose**<br><br>Most participants reported that they see a higher purpose in contributing to research; some even felt this was their main motivation to participate.<br><br>*"I would do it for my fellows."* | The sense of purpose in taking part in research could be enhanced and used as a motivational factor when informing potential participants about a trial.<br><br>The participants' commitment should be respected and validated at the end of a trial (see "aftercare" below). |

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|---|---|
| "*I do think it can be morale-boosting to feel that you are contributing in some worthwhile way and then understanding whether [the researchers] have gained any insights at the end of it can be validating.*" | |
| **Trust in the research team**<br><br>"*Becoming convinced of being in the sham group would be OK as long as I don't feel that something she should have known was omitted; I was informed about the possibility beforehand, so wouldn't take offence.*" | The distinction between blinding and lying may have to be clarified.<br><br>The ethical justification for the trial and trial oversight arrangements may be useful to communicate.<br><br>Unblinding at the end of a trial can be offered. |
| **Patient involvement in control development and trial preparation**<br><br>Knowing that patient representatives were involved in the development of a trial may mitigate many of the concerns presented above.<br><br>"*I'd assume from this [patient involvement] that simple things that would occur to me and other people like me may have been taken into account. That might not have been if it had been a group of young and keen researchers.*"<br><br>"*It's very beneficial for people living with pain to know that there is the acknowledgement of the value of that [involving patients]. That you are the kind of researcher that 'gets it' and has asked what it's like living with pain.*" | People with lived experience can anticipate many barriers to the successful conduct of a trial, including concerns peculiar to a controlled (as opposed to a comparative effectiveness) trial.<br><br>Involvement should commence early in the trial planning stage and involve people from the respective target population.<br><br>From a trialist's perspective, this also offers the opportunity to anticipate and test potential 'give-aways' for unblinding in the control arm. |

At the end of the hypothetical trial, all interviewees noted that they would have liked to find out which group they were in. They also discussed the desire for "aftercare," for example, being offered the opportunity to discuss their experience with a professional or even receiving (some amount of) the test treatment if shown to be effective. Offering additional treatment to participants in the control group could be a recruitment incentive. However, it also adds considerably to trial costs, may preclude longer follow-

up possibilities, and may not be desirable in the absence of efficacy and safety data. Nevertheless, with many trials failing to reach recruitment targets,[64] this may be a worthwhile investment for funders. As demanded by many funding agencies,[65] interview participants expected to be presented with the results of the trial, ideally in a manner understandable to lay members of the public.

## 4. Conducting a controlled trial

### *4.1. Fidelity monitoring and participant adherence*

**Essential recommendation item(s)**

- Providers' fidelity to intervention protocols and scripts should be monitored (if applicable).
- Participant adherence to and compliance with interventions should be monitored (if applicable).

*(CoPPS Statement and Checklist reference: 4.1)*

Fidelity monitoring refers to assessing whether interventions were delivered as specified by the intervention protocol. Participant adherence usually refers to participants' attendance of treatment sessions, while compliance means whether they completed the treatment as expected. Compliance can apply to both clinical visits and self-management at home.

**Example:** Kwekkeboom et al. [66] monitored the fidelity of a training session in pain self-management strategies using a fidelity checklist. Participants' use of the learnt techniques and their accessing of educational material provided as a control intervention were monitored using self-report diaries:

"*With permission, participant training sessions were audio-recorded and evaluated using a fidelity checklist […]. […] Participants [in the test intervention arm] were asked to practice at least one strategy per day, or more as needed, and log their use in a weekly diary. […] Participants [in the control intervention arm] were asked to listen to at least one recording per day, and to log their use in a weekly diary*."

### *4.2. Measuring participant expectation and blinding effectiveness*

**Essential recommendation item(s)**

- Provider expectations of benefit from the control versus the test treatment should be evaluated (if applicable).
- Participant expectations of treatment benefit should be assessed at baseline and after starting treatment sessions.
- Participant blinding must be assessed (if applicable).

*(CoPPS Statement and Checklist reference: 4.2)*

A large body of research on placebo effects has shown that participant expectations influence trial outcomes in a range of conditions, including depression and Parkinson's disease.[67,68] Evidence for a link between participant expectations and pain-related trial outcomes, however, is inconclusive and appears to partly

depend on the duration of the pain experience.[69,70] Assessing participant expectancy is also fraught with conceptual and practical challenges, and validated tools are sparse.[71,58,72] However, the potential implications of participant expectations and their dominant position in placebo research are arguments to routinely evaluate participant expectations at baseline and again after participants have started interventions,[73–75,69] whilst further developing measurement procedures [76] and scientific understanding in this area. Although treatment satisfaction is occasionally measured in clinical trials,[1] we warn against the use of satisfaction as a proxy for expectation effects or treatment credibility.

Provider expectations can be evaluated during the trial planning phase or after initial treatments and should be considered in light of Section 3.3.

Expectancy of treatment benefit and participant beliefs about group allocation are conceptually related but may differ when assessed. Assessing one does not substitute assessment of the other. Blinding effectiveness should be assessed by means of allocation guessing. Results of such assessment must be contextualised.[77] There is debate about the ideal time point of assessment, the potential of such assessments to influence expectations,[78] and the influence of treatment efficacy on allocation beliefs.[77] We consider 'successful blinding' to mean that a similar proportion of participants in the control and test group believes they received the test intervention or is unsure which intervention they received.[79,80] This can be assessed by James' or Bang's blinding indices[81,82] or by statistical tests that compare groups, such as Pearson's chi-square or independent t-tests. In any case, the underlying data of participants' guesses should be reported to allow for independent judgment of blinding success. Where it can be obtained, information about the reasons for participants' guesses can help contextualise the data and indicate whether treatment benefits in one group influence beliefs about allocation.[77]

Overall, we advocate for routine measurement of expectation of both benefit and blinding. Like all outcomes, these data should not be collected by the treatment providers. Information about whether enroled participants were treatment-naïve further helps with the interpretation of expectancy and blinding data.

**Example:** Developing and evaluating a novel control intervention for mindfulness meditation, Davies et al. tested blinding effectiveness and participant expectation of benefit:

"*We assessed credibility with a single-item manipulation check at the end of postintervention testing: "Do you think you were practicing a guided mindfulness meditation?" with respond options of "yes" or "no." Expectancy for pain relief was measured at baseline ("How effective do you think mindfulness is for reducing pain?") and after the first training session ("How effective do you think your training will be for reducing pain?") on a 100-point visual analog scale*."

### *4.3. Attrition*

**Essential recommendation item(s)**

- Reasons for participant withdrawal from the study should be documented.

*(CoPPS Statement and Checklist reference: 4.3)*

Despite being a required reporting item according to the CONSORT Statement,[62] information about reasons for withdrawal from the study is rarely adequately reported. The below examples show that, to be useful, reasons for participant withdrawal must be reported for each group individually. In addition, a level

of detail is required that allows one to make conclusions about the acceptability and credibility of the control intervention. It is also noteworthy that treatment discontinuation and study withdrawal are not necessarily the same, although they may be related and criteria for minimal treatment compliance may lead to the exclusion (withdrawal) of participants (See section 4.1 on compliance monitoring).

**Example 1:** While Coste et al. [83] report reasons for dropouts and differential attrition between groups, it remains unclear whether 'dissatisfaction' resulted from problems with the credibility of their control intervention, lack of perceived effects, or other factors:

"*Dropouts (due to patient dissatisfaction or non-adherence in 82% of cases) were observed at each stage of the study, but the dropout rate was particularly high before and during the first session. Moreover, dropout rates differed between the groups: 12/50 in the sham group versus 3/51 in the osteopathic group left the study early (p = 0.02, Fisher's exact test)*."

**Example 2:** Kwekkeboom et al. [66] report that gathering qualitative data about intervention acceptability may provide information about possible differences in attrition, even if lost participants cannot be contacted. Again, more detailed information at the group level would have been useful:

"*Negative reactions, including anxiety, sadness, unpleasant thoughts, boredom, and irritation, were reported by 11% of the CBS [cognitive-behavioral strategies] intervention group and by 21% of those receiving cancer education [i.e., the control intervention]."*

## 5. Reporting a controlled trial

For trial reporting, authors are referred to the amended TIDieR-Placebo checklist, available as part of the supplementary CoPPS 'toolbox' alongside this E&E document.

The following table (E&E Table 2) explains the items added by the CoPPS group and how they relate to TIDieR-Placebo.

**Table 2 (E&E): Essential reporting items for control interventions in trials of physical, psychological, and self-management therapies, in addition to all reporting items from TIDieR-Placebo**.[84] This table explains the rationale and content of the additional CoPPS reporting items. A complete hybrid checklist with TIDieR-Placebo is provided as a supplement. Given the amount of detail required to adequately report test and control interventions, some of this information may need to be reported as supplementary information to clinical trial reports.

| Reporting item | Explanation and relation to TIDieR-Placebo |
|---|---|
| *Control intervention development* | |
| Sources and processes that informed the development of the control intervention | Referencing of any consulted published literature and reporting of stakeholder involvement, consultation of other researchers, and testing procedures.<br><br>Reporting of this information is not covered by TIDieR-Placebo. |
| Theoretical considerations underlying the control intervention | Referring to conceptual discussions amongst the research team, including mechanistic considerations with regards to the 'principle of control similarity' (see above): Authors should report what they consider to be the components of the test intervention they intend to |

| | |
|---|---|
| | study. Conversely, authors should report what they consider to be the main components of the test intervention that are replicated by the control intervention.<br><br>Overlapping with item 2 of TIDieR-Placebo: "Describe any rationale, theory, or goal of the elements essential to the placebo/sham intervention."[84] The CoPPS recommendations add the need to make explicit mechanistic rationale and objectives of the control intervention, drawing on our guidelines for control development. |
| *Control intervention content* | |
| A highly detailed description of the content of the control intervention (covering all components listed in Table 3 of the CoPPS Statement, and including resemblance to or differences from the test intervention) | Descriptions of control interventions are usually brief.[1,85] A detailed description of all processes is recommended, potentially as a publication supplement. Journal editors should facilitate such supplementary information relevant to judge the quality of the trial and to inform future developments.<br><br>Overlapping with items 3, 4, 6, 7, 8, and 9 of TIDieR-Placebo, which cover materials, procedures, delivery modes, locations and settings, intervention amount, and tailoring, respectively.[84] There is an additional need to describe this explicitly in relation to the test intervention and provide a list of evidence-based components, as listed in Table 3 of the CoPPS Statement (Section 2.1). This should include a description of provider *behaviour*, verbal and non-verbal communication, and issues of equipoise, as detailed in the text of this guideline, as well as means to control these provider-related factors. |
| Provider characteristics and additional provider-related information | Item 5 of TIDieR-Placebo: "For each category of placebo/sham intervention provider (such as psychologist, nursing assistant), describe their expertise, background, and any specific training given."<br><br>Reporting should further include how issues of provider expectancy and allegiance 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 report test and control interventions, this must be reported along with differences in their characteristics. |
| *Control intervention quality* | |
| Whether any reasons for loss to follow-up (participant attrition) during the trial were related to the control intervention | Examples include non-acceptability or non-credibility of the control intervention, unblinding, control-related adverse events, and dissatisfaction.<br><br>Reporting of this information is not covered by TIDieR-Placebo. |
| Results of an assessment of blinding effectiveness | Ideally, these results should be reported as the number and proportion of participants in each group who thought that they received the test intervention, the control intervention, or were not able to guess ("do not know"), as well as the timepoint(s) of assessment.<br><br>Partly covered by TIDieR-Placebo, item 13 ("was blinding measured, and if so, how and what were the results of such measurement?"). In addition, blinding should always be assessed if it was an objective of the control intervention. Results should be reported as summary statistics per group, allowing independent calculation of blinding indices. |
| Results of an assessment of participant expectation | As discussed in the text, this should include the method of assessment, timepoints, and results as summary statistics per group. |

| | |
|---|---|
| | Reporting of this information is not covered by TIDieR-Placebo. |

## 6. Interpreting efficacy and mechanistic RCTs of PPS interventions

The CoPPS Statement makes several qualifying recommendations for the interpretation of efficacy and mechanistic trials. Interpretation can be complicated in PPS intervention trials, in part because the concept of efficacy is often ill-defined, not without problems especially in complex intervention research,[86] and trials exist on a spectrum from efficacy to effectiveness research.[87,12]

Nonetheless, interpretation is significantly aided by having and reporting a clear rationale for the choice of the studied treatment mechanism, as this determines the design of the control intervention and will help readers understand the study objectives. In addition, the resulting design choices will likely influence the observed clinical effects, and this may complicate translation into clinical or policy decision-making. An example from the field of acupuncture illustrates the potential challenges: mainly based on (so-called "sham") controlled trials, acupuncture was not recommended for low back pain or knee osteoarthritis in previous UK National Institute of Health and Care Excellence (NICE) guidelines, despite positive signals from trials comparing acupuncture to usual care. At the same time, different approaches to the design of acupuncture control interventions have led to conflicting results, with some trials effectively testing the traditional principles of acupuncture and others the effects of needle insertion. Adding to general concerns about the quality of acupuncture control interventions, this has led to criticism of systematic reviews and accusations that the resulting NICE guidelines 'mix apples and oranges'.[88–91] As control interventions improve and become more similar to tested treatments, this example also highlights challenges for evidence synthesis. Such synthesis requires conceptual clarity and transparent reporting from authors of primary studies and an awareness that effect sizes may differ from drug and comparative effectiveness trials.

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