

Guidelines for the Justification of Placebo-Controlled Trials

It is the responsibility of the researcher or sponsor to provide justification to the Clinical Trials Committee (CTC) for the choice of a placebo control group, as opposed to the other possible choices of control group (e.g., active control, wait-list control, dose-response and combination therapies). The criteria below are to ensure that this type of clinical trial design is used only in situations that do not compromise the safety and welfare of participants.

Article 11.2 of the Tri-Council Policy Statement, 2nd edition, states that:

- A new therapy or intervention should generally be tested against an established effective therapy.
- As with all alternative choices of a control, a placebo control is ethically acceptable in a randomized controlled clinical trial only if:
 - its use is scientifically and methodologically sound in establishing the efficacy or safety of the test therapy or intervention; and
 - it does not compromise the safety or health of participants; and
 - the researcher articulates to the REB a compelling scientific justification for the use of the placebo control.
- For clinical trials involving a placebo control, the researcher and the REB shall ensure the general principles of consent are respected and that participants or their authorized third parties are specifically informed (see Article 3.2):
 - about any therapy that will be withdrawn or withheld for purposes of the research; and
 - of the anticipated consequences of withdrawing or withholding the therapy.

Great care should be taken to avoid abuse of placebo comparators. They are, however, acceptable in any of the following situations:

1. There are no established effective therapies for the population or for the indication under study.
2. Existing evidence raises substantial doubt within the relevant expert community regarding the net therapeutic benefit of available therapies.
3. Patients are resistant to the available therapies by virtue of their past treatment history or known medical history.
4. The trial involves adding a new investigational therapy to established effective therapies: established effective therapy plus new therapy vs. established effective therapy plus placebo.
5. Patients have provided an informed refusal of established effective therapy, and withholding such therapy will not cause serious or irreversible harm.

The determination of response satisfaction and refusal of treatment must take place outside the context of recruitment for the clinical trial and prior to offering trial participation to the prospective participant, and both must be documented.

The use of a placebo comparator in situation (5) is permitted because prospective trial participants are not using established therapies and therefore are not benefiting from therapy.

For that reason, such participants would not be further disadvantaged if enrolled in a placebo-controlled trial than participants in a trial for whom there are no established effective therapies for the indication under study. Research proposals submitted to CTC must include sufficient support and justification of the trial design and use of placebo comparator.

Please ensure you refer to the applicable situation (1-5 above) when you answer justification for placebo question 9.0 on the Clinical Trial page in your IRISS application form.