

3.13 Use of Placebo or Wash-Out of Effective Therapy in Clinical Trials

1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for IRB review and approval of clinical trials that utilize placebos or wash-out of effective therapy.

2.0 Policy

- **2.1.** It is the policy of the Organization that use of placebo in a controlled clinical trial, or of a wash-out period from effective therapy, must be ethically and scientifically justified, and risks associated with placebo or wash-out must be minimized.
 - **2.2.** It is the policy of the Organization that subjects be adequately informed of the use of placebo or of wash-out of effective therapy, and of the associated risks.
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3.0 Definition

- **3.1.** Placebo is an inactive substance or treatment that may resemble an active medication or treatment, but has no therapeutic value.
The OHRP Institutional Review Board Guidebook Glossary defines placebo as "a chemically inert substance given in the guise of medicine for its psychologically suggestive effect; used in controlled clinical trials to determine whether improvement and side effects may reflect imagination or anticipation rather than actual power of a drug."
 - **3.1.1.** This policy refers use of a placebo in a RCT where the placebo is used as an alternative to the clinical intervention being tested (that is, intervention X vs placebo). The use of placebo when subject is also receiving the standard care (for example, standard treatment + intervention X vs standard treatment + placebo) generally does not pose an ethical concern in and of itself.
 - **3.2.** Randomization is assignment of subjects to different treatments, interventions, or conditions according to chance rather than systematically.
The OHRP Institutional Review Board Guidebook Glossary notes that "Random assignment of subjects to conditions is an essential element of experimental research because it makes it makes more likely the probability that differences observed between subject groups are the result of the experimental intervention."
 - **3.3.** Wash-Out Period refers to a protocol required period of withdrawal from current treatment prior to initiation of placebo or active treatment arms. "Wash-out" of effective therapy prior to institution of "investigational therapy" in a clinical trial may be ethically problematic, especially if the clinical trial includes a placebo arm.
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4.0 Ethical Justification

- **4.1.** The use of a placebo as an alternative to "standard therapy" may be ethically justified in the following situations:
 - **4.1.1.** There is no standard therapy.
 - **4.1.2.** Standard therapy is known to be not effective (that is, standard therapy is no better than no treatment).
 - **4.1.3.** Standard therapy may be effective, but associated with significant toxicity such that there is doubt regarding the net therapeutic advantage of the standard treatment.
 - **4.1.4.** Standard treatment is unavailable.
 - **4.1.5.** There are compelling and scientifically sound methodological reasons the use of placebo is necessary AND the patients who receive placebo will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention (WMA Declaration of Helsinki (2013)).
 - **4.2.** The use of a "wash-out" of effective therapy may be ethically justified when there are compelling and scientifically sound methodological reasons for the wash-out AND subjects will not be placed at additional risks of serious or irreversible harm during the wash-out period (or during the duration of the trial if subsequently assigned to placebo).
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5.0 Study Design Considerations

- **5.1.** The investigator must demonstrate, and the IRB must find that:

- **5.1.1.** The risk of placebo or of wash-out or effective therapy is minimized. Procedures to minimize risk may include, but are not limited to:
 - **5.1.1.1.** Careful and frequent monitoring for worsening of underlying condition
 - **5.1.1.2.** Early withdrawal of subjects for worsening of underlying condition, or for non-improvement
 - **5.1.1.3.** Early intervention or treatment (including, when appropriate, resumption of known effective therapy)
 - **5.1.1.4.** Exclusion of patients at increased risk of harm from wash-out, or non-response associated with placebo
 - **5.1.1.5.** Cross-over study design, where all subjects receive investigational treatment or intervention at some point in the study
 - **5.1.1.6.** Interim monitoring by DSMB
- **5.1.2.** Possible assignment to the active study drug offers the prospect of at least equivalent direct subject benefit compared to standard treatment.

6.0 Informed Consent Requirements

- **6.1.** For clinical trials utilizing placebo, the informed consent process and document must include:
 - **6.1.1.** A statement that a placebo is used in the study and an appropriate lay definition of “placebo” (for example “a pill or injection that has no medicine in it”).
 - **6.1.2.** The scientific rationale for use of a placebo, in lay terms.
 - **6.1.3.** The risks of non-treatment associated with placebo, including worsening of the subject’s disease or condition.
 - **6.1.4.** The plan for early withdrawal from the study if the subject’s clinical status worsens or fails to improve to a pre-defined level.
- **6.2.** For clinical trials utilizing wash-out of effective therapy, the informed consent process and document must include:
 - **6.2.1.** A statement that the research will utilize a wash-out period where subject will be taken off therapy that has been effective.
 - **6.2.2.** The scientific rationale for the wash-out period, in lay terms.
 - **6.2.3.** The risks of the wash-out period, including worsening of the subject’s disease or condition by discontinuing effective therapy.
 - **6.2.4.** The plan for early termination of the wash-out and resumption of effective therapy if the subject’s clinical status worsens.

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