Use of Placebos and Washout Periods in Research

Introduction:
The use of a placebo and/or washout in a research protocol, while justifiable in some circumstances, can be ethically problematic and should only be employed with specific valid reasons. Caution should be used when conducting a placebo-controlled trial and this methodology must be justified by sound scientific reasons. If currently existing therapy is life prolonging, or if placebo-recipients would be substantially more likely to suffer serious harm, use of a placebo is rarely, if ever, justified. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons, its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic, or therapeutic method;

- Where a prophylactic, diagnostic, or therapeutic method has been proven effective and is considered standard, but the toxicity or side effects and compliance with the standard treatment are such that subjects could substantially benefit from an alternative;

- Where a prophylactic, diagnostic, or therapeutic method is being investigated for a minor condition and the subjects who receive placebo will not be exposed to any additional risk of serious or irreversible harm, and denial of active treatment does not pose an increased risk of death, severe morbidity or disability, or severe discomfort.

Placebos may be used in clinical trials where there is no known or available (i.e. FDA approved) alternative therapy that can be tolerated by participants.

The Food and Drug Administration (FDA) has outlined its specific guidance on control groups and the use of placebo-controlled trials in an extensive guidance document issued in May 2001. (Guidance for Industry E10: Choice of Control Group and Related Issues in Clinical Trials)

Definitions:
Placebo is an inactive substance or treatment that may resemble an active agent or treatment but has no medical value.

Placebo-controlled Trial is a trial in which treatment with a placebo is compared with an active treatment or intervention to determine efficacy. A placebo-controlled trial can be single blind or double blind.
Washout Period is a period of time without active treatment, usually scheduled prior to initiation of placebo and/or active treatment arms. This can refer to a protocol required period of withdrawal from current treatment before active treatment starts.

Concomitant Medication refers to prescription and over-the-counter drugs and supplements a study participant is taking along with the study intervention.

Policy:
Protocols that use a placebo will receive full Board review. A placebo-controlled trial may be conducted with IRB approval provided that all the following criteria are met:

- The study is ethically justified.
- There is a clear and detailed rationale for the use of a placebo in the protocol.
- Potential risks are identified and minimized.
- The subject is adequately informed of the potential use and risks of the placebo in the study.

At the discretion of the Chair of the IRB, or at the request of the IRB, a protocol may be referred to the UHCMC Ethics Committee for consultative review prior to approval by the IRB.

Situations in Which Placebo is not appropriate:
A placebo arm is inappropriate whenever withholding an active (proven effective) treatment would increase the risk of more than minor harmful consequences or when minor or minimal harmful consequences due to withholding an active treatment or to the placebo itself are likely to be irreversible, or when there is no scientific justification for use of a placebo.

A) Protocol Requirements When a Placebo is used

The use of placebo controlled trials must be justified by a positive risk-benefit analysis. When submitting a protocol in which a placebo will be used, the investigator must:
1. justify the use of the placebo,
2. compare the use of placebo to standard therapy,
3. discuss risks associated with placebo use, including risk of worsening,
4. denote that subjects are not expected to receive benefit while on placebo, and
5. outline the methodology that will be used to minimize risks to subjects.

If vulnerable populations (children, decisionally impaired subjects, individuals with mental illness, pregnant women, etc.) are included in the study, the investigator must
provide additional details to justify inclusion and how subjects will be adequately protected. This is especially pertinent if the proposed use of placebo has the ability to adversely affect a subject’s ability to function and cause a subject to deteriorate at a more rapid pace than might be expected in subjects who are not considered “vulnerable”. .

The following are methods that can be used to minimize risks associated with the use of placebo and should be discussed in detail within the text of the protocol:

- Exclude subjects with an increased risk of harm from non-response.
- Include in the protocol increased monitoring for subject deterioration and the use of rescue medications.
- “Early escape” mechanisms and explicit withdrawal criteria should be built in so subjects will not undergo prolonged placebo treatment if they are not doing well.
- The size of the population placed on placebo may be smaller than the number in active treatment arms.
- Placebo and active treatment may be compared in an “add-on” method, keeping the subjects on identical maintenance treatments and then adding the active treatment to one arm and placebo to the other. This design is especially applicable when the available treatment is known to decrease mortality or morbidity.
- Shortened treatment periods reduce the risks associated with delayed treatment. In situations in which long-term placebo treatment would not be acceptable, the use of a placebo group for a short period at the beginning of a trial could establish short-term effects. The trial would then continue without the placebo group.
- Discuss risks associated with placebo use, including risk of worsening
- Recognize that subjects are not expected to receive benefit while on placebo
- Unblinded data review by a Data and Safety Monitoring Board with interim analysis of study results and safety issues. This is especially important for multi-center site studies.

**B) Informed Consent and Use of Placebo**

Participants must be fully informed of the use of placebo as part of the study and the possible risks, including discussion of exacerbation of current condition/symptoms as part of being assigned to the placebo group. The informed consent form must include the following information:

- A statement indicating that subjects may be given a placebo.
- A clear lay definition of the term “placebo,” such as “a pill/injection that has no active medicine in it,” “a sugar pill with no medicine,” etc.
- The rationale for using a placebo must be explained in lay terms to the subjects.
- If applicable, subjects must be informed of any viable medical alternatives to being placed on placebo.
The duration of time that a subject will be on a placebo, degree of discomfort, and potential effects of not receiving medication must all be explained.

Any consequences of delayed active treatment must be explained to the subjects.

A statement in the “Risk” section of the consent document that the subject’s condition may worsen while on placebo.

A discussion in the “Benefits” section that subjects who receive placebo are not expected to receive the same benefit as those who receive active treatment if that treatment is effective.

If all subjects are receiving active treatment throughout the trial, the above issues need to be addressed only for the placebo component of the trial.

**C) Protocol Requirements when Washout is Used**

Protocols that involve washout periods (with or without the use of a placebo) present similar concerns about risk to subjects as protocols using placebos because both involve withholding available, proven therapy from subjects. Therefore, similar attention should be paid to the justification of the use of a washout period including methods to minimize risks to subjects.

In order to determine if the washout period proposed is appropriate; the protocol must describe the following:

- The reason why active therapy is being withheld;
- The proposed duration of the washout period;
- If the washout period includes concomitant medication;
- The risks specific to this phase of the study;
- Details about subject safety monitoring that will occur during the washout period; and
- A discussion about what investigators will do if a subject experiences problems while off active treatment.

**D) Informed Consent and Use of a Washout Period**

Subjects must also be fully informed of the use of a washout period and any potential risks associated with this procedure. The informed consent form must include the following information:

- A statement indicating that the research will involve a washout period;
- A clear lay definition of the term “washout” (e.g. a period of time without any active medicine);
- The duration of time the subject will be asked to withhold treatment during the washout period;
- The risks associated with the washout period, including potential deterioration of the subject’s condition and/or exacerbation of the subject’s symptoms.
- Clear instructions to the subject stating who should be contacted if the subject experiences an adverse event during the washout period and what symptoms to watch for.

References and/or Regulatory Citations:


DHHS. Center for Drug Evaluation and Research, Center for Biologic Evaluation and Research. “*Guidance for Industry: Choice of Control Group and Related Issues in Clinical Trials.*”

FDA, *IRB Information Sheets, “Drugs and Biologics.”*

FDA, “*Guidance for Industry E10: Choice of Control Group and Related Issues in Clinical Trials.*” May 2001

OHRP IRB Guidebook, Chapter IV “Considerations of Research Design”

Related Policies:

*IRB Policy, Protocol Submission Requirements*
*IRB Policy, Ethics Consultation*