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GUIDANCE NOTES FOR PLACEBO-CONTROLLED TRIALS

INTRODUCTION

This guidance note describes the ethical duties pertaining to the use of placebos in research, and the minimum standards for using placebos in clinical trials.

GUIDANCE NOTE #1: DEFINITIONS

The TCPS 2 provides the following definitions:

Placebo is an inactive substance or treatment (e.g., a pill, an injection) given to participants to simulate an active substance or treatment. Often, the purpose of using a placebo as a comparator in a clinical trial is to control for the reaction participants may have to any kind of intervention and their beliefs about its possible effects. This may be done in order to distinguish the effects of the intervention of interest from the effects caused by participant belief. It may also be used as a control to distinguish effects of the intervention of interest from the natural background rate of symptoms or variability in a disease that occurs in a population.

Placebo-controlled trial – A clinical trial in which the safety or efficacy of one or more interventions are compared with a placebo control group.

GUIDANCE NOTE #2: USE OF PLACEBOS

The decision to use placebo comparators in clinical trials raises specific ethical issues for participants, including potentially depriving participants of needed therapies and/or causing a worsening of their condition. As such, a clear and compelling scientific justification that prioritizes participant safety and wellbeing must be provided for any clinical trials proposing a placebo comparator.

Where possible, alternatives to placebo use should be employed. However, placebo arms may be acceptable in 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. Available therapies are known to be ineffective for patients by virtue of their past treatment history or known medical history.

4. The trial involves adding a new investigational therapy to established effective therapies: e.g. testing an established effective therapy plus new therapy against established effective therapy plus placebo.
5. Patients with decision-making capacity have provided an informed refusal of established effective therapy, and withholding such therapy will not cause serious or irreversible harm.

GUIDANCE NOTE #3: REQUIREMENTS FOR SUBMISSION

In order for the REB to approve the use of placebo-controlled trial, the following criteria set out in Article 11.4 of the TCPS 2 must be satisfied:

A new therapy or intervention should generally be tested against an established effective therapy. A placebo control is ethically acceptable in a randomized controlled clinical trial only if:

a) its use is scientifically and methodologically sound in establishing the efficacy or safety of the test therapy or intervention;
b) it does not compromise the safety or health of participants;
c) the researcher articulates to the REB a compelling scientific justification for the use of the placebo control; and
d) the general principles of consent are respected and participants or their authorized third parties are specifically informed (Article 3.2) about:
    - any intervention or therapy that will be withdrawn or withheld for purposes of the research; and
    - the anticipated consequences of withdrawing or withholding the intervention or therapy.

The study protocol must provide:

- a clear and compelling scientific justification for the placebo use;
- a detailed explanation of the safety measures to minimize risks to participants;
- provisions for appropriate care and follow-up for participants on the placebo arm; and
- a monitoring plan for adverse events and/or changes in health status.

In addition to the protocol requirements, the consent form must clearly define a placebo in lay language and detail the risks related to those assigned to the placebo arm, including the potential for their condition to worsen.
