Use of placebo controlled trials

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Context

The introduction of Clause 29 on use of placebo in the 5th revision of the Declaration of Helsinki has generated much discussion over the years. This stated that new treatments should be tested against best current treatment rather than placebo. The clause was formulated in response to sustained criticism of field trials in developing countries that tested short course therapies aimed at preventing vertical transmission of HIV using placebo controls but has been controversial. As an example, Tollman wrote that ‘this revision may harm the interests it intends to protect’[1]. He noted that there were weak health and public sector systems in much of the world were already subject to unparalleled demands. Clause 29 could impose demands on local and national health systems that, without massive additional investments, simply could not be met. While not arguing that ethical standards have to be compromised, he endorsed that that ‘considerations of context are required aspects of moral reasoning in the application of universal principles to specific situations.’

The current Declaration of Helsinki refers to the Use of Placebo in clinical trials in Clause 33 and states:

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

   Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

   Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

   and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

   Extreme care must be taken to avoid abuse of this option.

Thus, the use of placebo is acceptable when there is no proven intervention for the condition under study and there can be circumstances when a placebo is justifiable even when a proven therapy exists. However, what constitutes compelling and scientifically sound methodological reasons for use of placebo is not defined and could be subject to varying interpretation by individuals and bodies concerned in the design, review and approval of trials.

Keränen et al. noted that patients asked to participate in RCTs often have difficulties in understanding the meaning of the concepts involved and the justification for the procedures[2]. They conducted a study to evaluate how well the justification for the use of placebo had been described in the RCT protocols and by the principal/national co-ordinating investigators. From a review of 52 RCT protocol and associated documents, they concluded that the justification of placebo control was inadequately described in many RCT study protocols, by principal or national co-ordinating
investigators, and in participant-information documents. Possible health-related risks associated with the use of placebo were poorly explained in the participant-information documents. They agreed with Bishop et al.[3] that there is a clear ethical need for greater transparency and more respect for the participants in the provision of written information about placebos and considered that ethics committees and study participants needed to be better informed of the rationale for the use of placebo, along with the associated risks.

Guidance from Good Pharmaceutical Medical Practice

Pharmaceutical doctors are frequently involved in the conduct of clinical trials, either as sponsor representative or clinical investigator. You must ensure that the clinical trial has a reasonable probability of successfully answering the research question. The intervention in the clinical study must be justified.

In applying the principles from GPMP and experiences gathered from reviewing RCT documentation; pharmaceutical physicians conducting clinical trials should ensure that justification of placebo control is well described in study protocols. Ethics committees and study participants need to be well informed of the rationale for the use of placebo, along with the associated risks.

Reading list

