

Background: Ever since the 1996 revision of the Declaration of Helsinki, the World Medical Association has attempted to address ethical and scientific concerns of its diverse stakeholders for Articles 33 (use of placebo) and 34 (posttrial provisions), most recently in 2013. Both are inextricably linked to standard of care, an essential element of any comparative, interventional clinical trial. But has this now 20-year-long ethical debate truly been put to rest? The choice of standard of care in clinical trials remains a complex issue, particularly for comparative trials conducted in emerging countries. Interpretations of the Declaration of Helsinki as the cornerstone document for medical ethics range from best intervention available worldwide to any locally available standard of care for the comparator group, which in the worst case could mean no interventional care at all.^{1,2}

Objectives: Our aim was to examine the current status of clinical research practice and ethical guidance on standard of care, with a focus on international health research, and to review corresponding guidance issued by pharmaceutical sponsors in their publicly accessible policies on clinical research.

Methods: We reviewed ethical recommendations before and after 2013 and scientific literature, as well as major clinical trial registries (European Union, United States, and World Health Organization), to assess current clinical research practice related to standard of care. Furthermore, the websites of the top-ranked 25 pharmaceutical companies on sales figures in 2014³ were reviewed for publicly accessible policies with reference to standard of care in clinical trials in emerging regions.

Results: After a period of active scientific-ethical debate before the 2013 revision of the Declaration of Helsinki, few ethical discussions or recommendations have since been published that could provide additional guidance to clinical researchers. The recent scientific literature reflects the continued challenge for researchers to design an ethically and scientifically sound study, especially in vulnerable populations. However, ~20% of registered open clinical trials across major trial registries are designed with a placebo control, suggesting that the question of standard of care remains highly pertinent. The review of pharmaceutical sponsor websites revealed a highly variable picture with regard to publicly available policies or statements on this issue, particularly for research conducted in low- to middle-income countries. The review outcome spans results from any policy published to very clearly worded statements on clinical research in developing countries, the standard of care aspect during the trial conduct, and regulatory strategies after completion of product development.

Conclusions: Investigators, ethics committees, and sponsors continue to be confronted with the challenge of ensuring ethically and scientifically sound clinical studies with appropriate standard of care. We have attempted to examine available ethical guidance and summarize recommendations for clinical trial designs that could assist in addressing these challenges. Care should be taken to maintain a high level of awareness for the importance of a sound ethical framework for a scientifically valid clinical trial design. Pharmaceutical companies, as major sponsors of clinical research, should demonstrate awareness and an appropriate management of these aspects, particularly in regions with limited resources. As part of the ongoing debate on transparency, one option could be to formulate positions and make them available to the public, regardless of whether such a statement is legally required. A few examples already exist where such clarifying statements have been provided. This approach would prepare the ground for an open and transparent communication to agencies, ethics committee, and, last but not least, patients.

Key words: bioethics, clinical research, Declaration of Helsinki, international health research, placebo, standard of care.

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CLINICAL RESEARCH AND STANDARD OF CARE—AN UNRESOLVED QUESTION?

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