Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORS' CHOICE

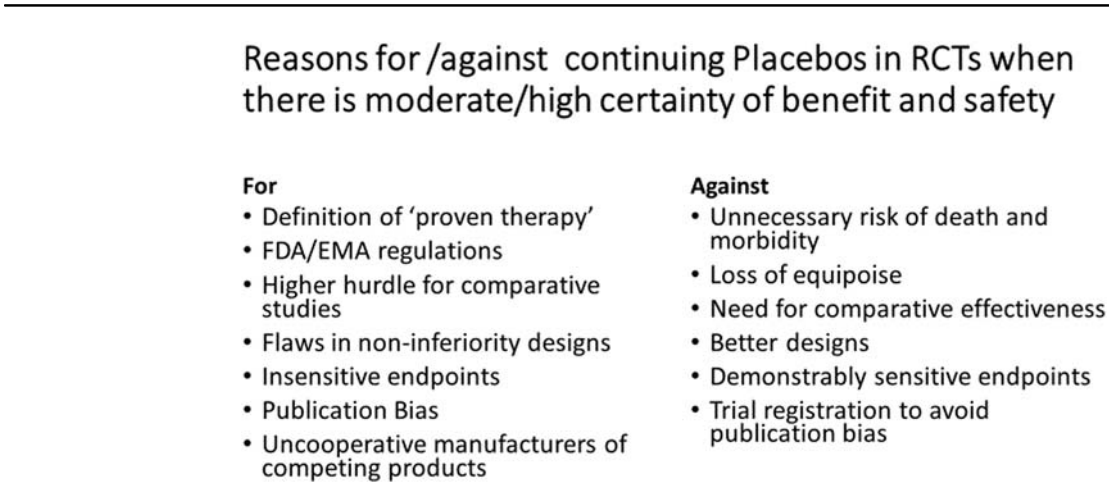
In 2021 When Is It Unethical to Use a Placebo in a Clinical Trial?

Two articles in this issue focus on this question. Paragraph 33 of the 2013 World Medical Association Declaration of Helsinki [1] states "The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best proven intervention". Elaborating statements include statements to the effect that use of a placebo as a comparator is only ethically justified when there is no proven effective intervention, or there are no harms from delaying or forgoing treatment. In this issue, Afach et al review this question in clinical trials of therapies of psoriasis; there is robust evidence that there have been efficacious and effective therapies for over 20 years now. Despite this over 75 % of 22 trials continue to include placebo arms [over 7000 patients in placebo arms; the patients in the placebo arm are therefore being denied effective treatment and there is no ethical rationale for this − the trials must be in breach of the Declaration. In a second article on this topic Knottnerus discusses the issue of placebo trials in the context of COVID-19 vaccine trials, where, again, it is now clear that a number of vaccines have demonstrated impressive efficacy, yet many thousands of individuals in ongoing trials continue to be allocated to the placebo arm.

The arguments have been well described but are worth summarising, given this surprising reluctance to adopt the Declaration of Helsinki recommendations:

The rationale to justify the continuing use of placebo groups include a] arguments about how the term 'proven therapy' used in the Declaration of Helsinki is defined. This needs to be the net benefit i.e. the advantages outweigh the adverse effects; b) regulatory requirements applied by organisations such as the FDA, for any new drug or biologic molecule, and the European Medicines Agency, for conditions where the condition fluctuates; c] the perceived practical and financial benefit of permitting a smaller sample size because of the greater expected effect size plus the ability to include only 2 trial arms; d) the concern that forbidding placebo trials puts the manufacturer of a new treatment at a disadvantage in having to demonstrate superiority relative to an existing treatment which is much harder than demonstrating benefit compared to placebo; e)concerns about equivalence and non-inferiority designs; f) concerns about the responsiveness of the outcome measures to detect and provide robust estimates of minimal clinically important differences for both benefit and harms; g) publication bias given that many negative studies do not get published; g) challenges of obtaining cooperation between companies making the different products.

The rationale for not using placebo controls, and focussing on head to head comparative trials once there is moderate or high certainty of benefit and safety include a) unnecessarily exposing the placebo patients to the morbidity and mortality of the underlying condition that would be avoided with proven treatment; b) loss of equipoise means that it is unethical to withhold a therapy of known efficacy from any patient in a trial i.e. in a placebo group even in a trial with several active treatment arms; c) clinicians and patient need comparative information, not comparisons against placebo, to make informed decisions on the



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alternative options for treatment; d) the ability to permit longer duration trials given all patients are receiving active treatment; e) advances in clinical epidemiology metrics are now available to ensure unbiased study design and implementation with demonstrated responsiveness of the clinically patient-important endpoints. f) trial registration should now address the issue of publication bias

After reading these two articles in this issue we would welcome hearing the views of readers in our correspondence to comment on how to ensure better adherence to the Declaration of Helsinki.

Peter Tugwell
David Tovey

References

[1] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.