

Thorax protocol review: working with trialists to improve trial quality

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The purpose of clinical trials is to evaluate the safety and efficacy of treatment interventions such as drugs, devices and diagnostic tests. It is therefore essential for the safety of those receiving these interventions, as well as for scientific integrity, that these trials are conducted according to a protocol that is scientifically and ethically sound. The importance of a properly designed trial was recognised in the early years of modern clinical research as demonstrated by the works of Sir Ronald A Fisher in his *Principles of experimental design* in the 1920s.¹ The first randomised trial in 1946 investigated the effectiveness of streptomycin for TB.² Since then, the methodological rigour of clinical trials has continued to improve. Recent notable improvements include the prospective registration of trials (which is now a requirement for research ethics approval in the UK),³ efforts to improve trial protocols,⁴ standardisation of the definitions of interventions⁵ and outcomes,⁶ as well as improved reporting of clinical trials.⁷ More recently, in the setting of evidence that the reporting of clinical trials is not consistent with the trial protocol, the role of full protocol publication is increasingly recognised.⁸

The process of protocol publication has various benefits including an improvement in the standard of reporting in medical research.⁹ *Thorax* is now offering protocol review for authors. Authors will have the option of submitting their protocol for peer review and benefit from expert opinion on their trial design with the potential for publication of the trial protocol in the *BMJ Open* or *BMJ Open Respiratory Research*. They will also benefit from rapid peer review of their main trial paper if submitted to *Thorax*. Further details can be accessed by referring to the online instructions to authors for *Thorax*.

There are obvious advantages to authors and the scientific community

from the publication of trial protocols.¹⁰ These include mitigating publication bias (by reducing under-reporting of trials)¹¹ and prevention of data dredging by publishing only a priori defined analyses.

A key question to consider is how the peer-review process can add further value to protocol publications and how researchers might benefit from this service, without adding additional challenges. It is notable that *The Lancet* has recently withdrawn its protocol review service,¹² and in the nearly two decades during which *The Lancet* offered protocol review, only 148 protocol summaries were published. Peer review is considered as a quality assurance of a publication but has its limitations. The review process is subjective and methodological flaws may be overlooked at review.¹³ Steps taken to improve the review process have shown conflicting results.¹⁴ In addition, a trial protocol is often submitted when the trial has commenced. The challenge of how changes mandated as part of the peer-review process of the trial protocol can be made in the setting of a regulatory authority-approved protocol needs to be considered. Researchers might be reluctant to submit the study protocol prior to regulatory approval given the potential delays this might cause with the trial commencing.

To ensure that this valuable process is widely adopted and used, several additional points should be considered. One of the key benefits from this protocol review service is the expert input into trial design. As highlighted above, submission of the protocol to this review process should occur prior to the trial commencing. Peer review should identify flaws in the protocol and suggest steps to overcome the flaws. Early identification of methodological flaws will give the opportunity to incorporate the changes and deliver a higher quality trial. A key issue will be the speed with which the protocol review is undertaken so that it does not add any delay with regulatory approvals and the trial commencing. Ideally, the same reviewer should review the trial protocol and the main trial paper, which will help reduce the burden on the reviewer as well as improve consistency. A scheme to enable this to be achieved

should be considered even if the main trial is not submitted to the journal group accepting the protocol. One option to achieve this would open peer review where the researchers could recommend the same reviewer for the subsequent publication of the main paper. An outline statistical analysis plan should be published in the trial protocol to ensure that the published analyses are faithful to the protocol defined a priori analyses. A more detailed statistical analysis plan should be submitted with the paper as an online supplement. It is recognised that this may not be available at the time of the protocol submission and could be submitted after the protocol paper is published. Finally, publication of the trial paper should be dependent on the trial conduct and methodology, and not the results. This will significantly reduce publication bias against trials with negative results and reduce under-reporting. This is a key part of the commitment by *Thorax* to authors who submit their protocol for review.

Peer review and publication of protocols are important steps in the process of improving the quality of clinical trials. While this is not necessarily a guarantee that the trial will be well conducted, it should improve the quality of our clinical trials.

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