Megatrials of Drug Treatments: Strengths and Limitations

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Abstract

Introduction**: Megatrials are large-scale randomised controlled clinical trials recruiting thousands of patients from large numbers of trial sites with the aim of providing reliable evidence on clinical outcomes of treatments. This review describes the characteristics, strengths and limitations of megatrials. **Methods**: Review of the literature on methodology of megatrials was performed after searching the MEDLINE database. **Results**: Megatrials are based on a pragmatic trial philosophy, and usually feature broad eligibility criteria, simple trial design, uncomplicated treatment regimes, routine clinical monitoring and adjunctive care, and streamlined data collection on clinical outcomes. An intention-to-treat analytical approach is normally used. The main strength of the megatrial is its ability to reliably detect moderate differences in important clinical outcomes. Biases are avoided by utilising the principles of randomised treatment allocation, blinding where possible and objectivity in assessment of outcomes. The megatrial is able to more precisely estimate treatment effects by using data from large numbers of patients. Results can be more readily generalised because of the wider spectrum of patients studied. Also, megatrials have an advantage over meta-analysis in that there is less heterogeneity. The assumption of qualitative homogeneity of effects underlying the interpretation of megatrial results is reasonable with proper selection of the trial population. Complex clinical and non-clinical outcomes are difficult to measure in megatrials. Hence, megatrials are unable to provide much insight into the mechanism(s) of action of drugs. Smaller explanatory trials or sub-studies designed to provide biological insight could usefully complement megatrials. **Conclusion**: Megatrials can provide reliable large-scale randomised controlled clinical trial (RCT) evidence of moderate treatment benefits. They are well complemented by smaller explanatory trials.

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