

Megatrials of Drug Treatments: Strengths and Limitations

D Heng,*^{MBBS, MRCP (UK), MPhil (Epidemiol)}

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.

Ann Acad Med Singapore 2000; 29:606-9

Key words: Clinical epidemiology, Drug evaluation, Evidence-based medicine, Megatrials, Randomised controlled trial

Introduction

A “megatrial” is a very large randomised controlled clinical trial (RCT) recruiting many thousands of patients from many centres in order to assess the effectiveness of treatments on clinical outcomes. Examples of megatrials which successfully recruited more than 10,000 patients include the International Studies of Infarct Survival (ISIS) series of trials,¹⁻⁴ Gruppo Italiano per lo Studio della Streptochinasi nell’ Infarto Miocardio (GISSI-I),⁵ the International Stroke Trial (IST),⁶ and Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I).⁷

The concept of “large, simple trials” featuring a pragmatic trial philosophy,^{8,9} a simple trial design and minimal data collection, has been strongly advocated by Yusuf, Peto and colleagues.¹⁰⁻¹² It was first used in the ISIS-1 trial¹ in the early 1980s. Since then, megatrials have evolved in terms of size and complexity, but nevertheless, most retain some characteristics of the original concept.

Characteristics of Megatrials

The characteristics of megatrials (Table I) are shaped by

the need to recruit large numbers of patients on the one hand and limitations of resources on the other, and hence, may differ considerably from a typical phase III RCT in the context of the drug development process.

In order to recruit large numbers of patients, megatrials are necessarily multicentre, involving a large number of clinical sites and often simple, broad eligibility criteria are used. There is usually no requirement for extensive pre-trial tests on patients or placebo run-in periods. Reliance is placed on the underlying principle that patients are eligible for the trial as long as there is substantial uncertainty as to which of the treatments being compared is better for them. In contrast, a typical phase III RCT during drug development has narrow, rigidly specified eligibility criteria, with eligibility often defined on the basis of extensive pre-trial investigations and compliance during a run-in period.

In the quest for size in the face of resource limitations, a pragmatic trial philosophy,^{8,9} and relative simplicity is favoured. The protocol algorithm and treatment regime is usually uncomplicated, and monitoring of the patient is not increased above the norm for clinical practice. No extra monitoring investigations beyond that used in routine

* Clinical Epidemiologist

Clinical Trials and Epidemiology Research Unit, National Medical Research Council, Singapore

Address for Reprints: Dr D Heng, National Medical Research Council, Clinical Trials and Epidemiology Research Unit, 10 College Road, Singapore 169851.

TABLE I: CHARACTERISTICS OF MEGATRIALS

-
- Large number of patients
 - Large number of clinical sites
 - Simple trial design
 - Broad eligibility criteria
 - Uncomplicated trial protocol
 - Streamlined data collection
 - Clinical outcomes
 - Intention-to-treat analysis
-

clinical practice is usually required. Adjunctive care and treatment are often not rigidly specified by the trial protocol and left to the discretion of the attending physician. “Hard” or easily defined clinical outcomes (e.g. death) are studied, and data collection is streamlined to the minimum necessary to meet the objectives of the trial by keeping the complexity and number of follow-up forms to a minimum. Thus, conduct of the trial adds little or nothing to the existing workload of clinicians. This can again be contrasted with a typical phase III drug development RCT protocol that rigidly specifies adjunctive care, mandates intensive monitoring and collects massive amounts of data.

The analytical approach used is invariably on an intention-to-treat basis, where patients are analysed based on the group they are randomised to, regardless of the treatment actually received, compliance, subsequent withdrawal from therapy, or other “protocol violations”.

Strengths (Table II)

The main strength of the megatrial and indeed its *raison d’être* lies in its ability to reliably detect moderate differences in important clinical outcomes. In many situations, it is unrealistic to expect large gains in therapeutic efficacy from treatments tested. For example, the use of thrombolysis, considered a paradigm shift in the treatment of acute myocardial infarction, results in modest relative risk reduction of the order of 20% and absolute risk reduction of the order of 2% to 3% in mortality terms. However, even a moderate relative risk reduction in major outcomes may well translate into savings of millions of lives world-wide, particularly in the case of common diseases. In order to

TABLE II: STRENGTHS OF MEGATRIALS

-
- Aims to detect moderate differences
 - Avoids selection and assessment biases
 - Less heterogeneity of trial population, treatment regimen and data collected compared with meta-analysis
 - Clinical rather than surrogate outcomes studied
 - Generalisability
 - Sub-group analysis/detect effect modification
 - Convincing and able to change clinical practice
-

detect moderate treatment benefits reliably, it is obvious that biases and random errors must be kept small.

Biases are avoided in the megatrial, as with other randomised controlled trials, by utilising the same principles of randomised treatment allocation, blinding where possible and objectivity in assessment of outcomes. In contrast, non-randomised designs such as patient database studies and studies using historical or literature controls are prone to bias when used to study comparative treatment efficacy or effectiveness. This is because the allocation process is invariably influenced (whether explicitly or implicitly) by factors which also affect patient outcome. For example, in a historically controlled study, the treatment allocated depends on what treatments are available in the calendar period in which the patient presents, but other factors that affect outcome may also have changed over time (e.g. quality of nursing or adjunctive care). In a patient database study, the treatment allocated is based on physician clinical judgement and preference. However, this may well result in treatment groups with different prognosis, as for example, when a “less well tolerated” treatment is prescribed mainly to young and fit patients. It should be noted that increasing the size of the study does not reduce such biases.

Formal statistical hypothesis testing during the analysis sets a limit on the probability of wrongly getting a positive trial result. However, it is also important to detect a true treatment difference when it really exists. The megatrial is able to detect moderate treatment difference by using data from large numbers of patients.

Many empirical studies have shown that in the past, small trials were unable to reliably detect moderate treatment effects. Such “under-powered” trials may result in premature abandonment of promising therapies. With increasing recognition of this problem, methods of meta-analysis for combining results of many small trials of similar design have been used to increase power. Megatrials have an advantage over meta-analysis in that there is less heterogeneity in terms of patient population, treatment regimen and data collection, because of the use of common eligibility criteria and a common trial protocol. Studies included in a meta-analysis may be very heterogeneous in terms of baseline clinical features of patients, details (e.g. dose, frequency, duration) of the principal treatment studied, comparator treatments, and outcome measurement. In addition, bias in the selection process for study inclusion is an important issue in meta-analysis that is not present in megatrials.

The use of clinical outcomes (e.g. survival, major morbidity) rather than surrogate outcomes (physiological/biomedical e.g. CD4 cell count in HIV infection, glycosylated haemoglobin in diabetes, left ventricular ejection fraction in heart failure) is a hallmark of megatrials. This is because,

often, only megatrials have sufficient power to detect moderate differences in clinical outcomes. Surrogate outcomes can be studied in smaller studies of shorter duration. However, surrogate outcomes can be misleading if not well validated. The ultimate aim of treatment is to make a difference to the patient in terms of clinically relevant outcomes.

In contrast to explanatory trials, megatrials usually adopt a strategy of recruiting from a broad spectrum of patients, with wide eligibility criteria. This is a strength in that results can be more readily generalised. The use of multiple centres (often not confined to highly specialised tertiary centres) also gives an opportunity to assess the true effectiveness of treatments on the frontline, in everyday clinical practice in secondary or even primary care centres.

A question often posed by clinicians is whether the response to treatment is affected by any particular patient characteristic. Such questions concerning effect modification can be answered reliably only with large sized trials, such that even within a particular sub-group of interest, there is sufficient data for a meaningful analysis of outcome.

Ultimately, the results of well-conducted megatrials have been convincing to clinicians and have resulted in changes in clinical practice. For example, results from megatrials have led to the widespread use of beta-blockers,¹ fibrinolytic agents,^{2,5,13} aspirin,^{2,13} and ACE inhibitors⁴ in the treatment of acute myocardial infarction. In some cases, the results of previous small trials have been negated (e.g. usage of magnesium sulphate in acute myocardial infarction).⁴

Limitations (Table III)

One assumption underlying the interpretation of megatrial results is that of qualitative homogeneity of effects. In other words, the assumption is made that if treatment A is better than B, this result holds true in all sub-groups studied, although it is accepted that the magnitude of the benefit may well differ. Certainly, real life examples can be found where this assumption does not hold. For example, if patients with stroke are included in a megatrial based on clinical signs alone without the use of CT scan evaluation, the effect of warfarin might be expected to be very different in strokes of ischaemic as opposed to haemorrhagic origin.

However, with care in the selection of the study population and eligibility criteria, this assumption can be a reasonable one.

Although megatrials study a broader population compared with other types of clinical trials, the trial population is still a relatively selected one. This is unavoidable because of the ethical obligation to seek informed consent from trial participants and to exclude patients for whom one of the treatments being studied is particularly indicated or particularly dangerous.

Megatrials have been criticised on grounds of lack of methodological rigour because of the relative simplicity of the eligibility criteria, treatment protocol, monitoring and data collection procedures. Their defenders argue that by concentrating on the important issues, namely avoidance of bias by the use of random treatment allocation and improving power to detect moderate treatment difference by collecting large-scale evidence, megatrials have been able to provide reliable estimates of the effectiveness of treatments. In contrast, insistence on rigid control of every aspect of the trial would have made conducting such large-scale trials almost impossible in practice because of the resources and costs involved.

Intention-to-treat analysis in the face of treatment modifications or even discontinuation, non-compliance, withdrawal, and other “protocol violations” can lead to a trial result that underestimates the theoretical efficacy of the drug under ideal conditions. However, this is reflective of the actual practical effectiveness of the drug, because in real life, patients do default, forget to take their medication or “violate” the doctor’s instructions to them in other ways.

Individual megatrials may well suffer from defects in methodology. “Megatrial” status does not automatically mean that a trial is well designed, although this is arguably more likely because there would often be a good mix of viewpoints and expertise in the trial team in view of the large amounts of resources being expended.

Due to the large trial size and resource limitations, sophisticated and complex clinical and/or non-clinical outcomes are difficult to measure in megatrials. For example, quality-of-life type outcome measures are seldom used in megatrials. Most megatrials have concentrated on “hard”, easily defined outcomes such as death.

Because of the emphasis on clinical outcomes and the difficulties in measuring complex physiological or biochemical outcomes, megatrials are unable to provide much insight into the mechanism(s) of drug action. Some megatrials have addressed this problem in sub-studies involving a sample of the trial population in selected centres. In these sub-studies, more complex measurements are made in order to investigate such questions of biological mechanism. Smaller explanatory trials designed to provide

TABLE III: LIMITATIONS OF MEGATRIALS

-
- Assumption of qualitative homogeneity of effects
 - Relatively selected population
 - Simplicity in trial design
 - Difficult to study complex outcomes
 - Lack of insight into biological mechanism of drug action
 - Require large amounts of resources
-

biological insight can also usefully complement megatrials.

A megatrial is a hugely expensive undertaking in monetary terms as well as in its demands on resources (e.g. the GUSTO trial cost about USD 100 million). Hence, megatrials are not usually used to fine-tune dosages or treatment strategies. This is another area where smaller explanatory trials using intermediate endpoints have a role to play.

Conclusion

Megatrials are extremely useful for providing large-scale RCT evidence of moderate differences in hard clinical outcomes between treatments. However, their limitations should be borne in mind, and they are usefully complemented by smaller explanatory trials, which can be used to fine-tune dosages or treatment regimens as well as to provide valuable insight into the biological mechanisms of action of drugs.

REFERENCES

1. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet* 1986; 2:57-66.
2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988; 2:349-60.
3. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992; 339:753-70.
4. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 1995; 345:669-85.
5. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986; 1:397-402.
6. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997; 349:1569-81.
7. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993; 329:673-82.
8. Armitage P. Attitudes in clinical trials. *Stat Med* 1998; 17:2675-83.
9. Roland M, Torgerson D J. What are pragmatic trials? *BMJ* 1998; 316:285.
10. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984; 3:409-22.
11. Baigent C. The need for large-scale randomized evidence. *Br J Clin Pharmacol* 1997; 43:349-53.
12. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol* 1995; 48:23-40.
13. Collins R, Julian D. British Heart Foundation surveys (1987 and 1989) of United Kingdom treatment policies for acute myocardial infarction. *Br Heart J* 1991; 66:250-5.