Editorial

Are there fundamental deficiencies in the megatrial methodology?

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Does size matter? Is big beautiful? The triumph of the megatrial suggests that this is so, but Bruce Charlton, in a provocative paper entitled 'Fundamental deficiencies in the megatrial methodology', challenges this current conventional wisdom [1]. He sides strongly with clinicians by pointing out that one purpose of clinical trials is to provide meaningful and useful information that could be easily translated into clinical practice.

One of his major objections to the megatrial is the assumption that patients recruited into them are homogeneous. This idea has always been difficult for down-to-earth clinicians to accept, because they know that in myocardial infarction, for example, there is a huge difference in prognosis between the elderly hypotensive patients and young normotensive ones. Thus, when Peel of Glasgow created his prognostic index in 1962, patients could be categorised into groups whose mortality at 28 days ranged from 3% to 88% [2]. One of the sad truths about even the largest megatrials is that they are too small - that is, they are not big enough to tell us much about subgroups. Another sad truth of large simple trials is that simplicity is typically accomplished by not collecting clinical data that would allow analysis of important subgroups. Indeed, we keep being told that subgroup analysis is hazardous. While this is undoubtedly true, it has led to the unfortunate mindset that because subgroup analysis is dangerous, subgroups do not exist. This is incredible to clinicians and is one the reasons why practitioners do not implement the 'results' of trials.

However, there are megatrials that have rightly changed practice dramatically. Perhaps the most obvious example is the International Study of Infarct Survival (ISIS)-2 which demonstrated not only that streptokinase and aspirin were each capable of having a major impact on the fatality of myocardial infarction, but that they were additive in their effects. It is questionable whether we would have obtained this information without a trial of great size.

Our hope is that Bruce Charlton, through his paper, will stimulate constructive discussion and critical self-evaluation that will improve communication between clinical trialists and practicing clinicians.

One can conclude that we should be very careful in our interpretation of the results of megatrials. In applying the findings of trials in practice, clinicians should continue to take into account their own experience and that of others and the biological plausibility of the findings, and they should use common sense.

References

1. Charlton BG: **Fundamental deficiencies in the megatrial methodology.** *Curr Control Trials Cardiovasc Med* 2001, **2**:2–7.
2. Peel AAF, Semple T, Wand I, Lancaster WM, Dall JLC: **A coronary prognostic index for grading the severity of myocardial infarction.** *Br Heart J* 1962, **24**:745–756.

To comment on Bruce Charlton's article, "Fundamental deficiencies in the megatrial methodology" (pages 2–7), or any other article, please write to the Editorial Office.