**LARGE, SIMPLE TRIALS**

From the Therapy chapter for the 3rd edition of Clinical Epidemiology, by DL Sackett
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In 1984, Salim Yusuf, Rory Collins, and Richard Peto provided the scientific and pragmatic basis for large, simple trials[1]. They presented 4 powerful arguments in their rationale:

1. For the major killing diseases, any treatment of overwhelming efficacy would have shown itself long ago, and wouldn't need an RCT of any size to prove it. Moreover, patients with killing diseases die through a variety of mechanisms, and we shouldn't expect any single treatment to influence more than one of them. We therefore must look for only moderate but worthwhile effects of new treatments, say relative risk reductions (RRRs) for death in the range of 25%. Although this might not seem an important accomplishment, if one-tenth of a million women with coronary heart disease were likely to die in the next five years, a treatment with a relative risk reduction (RRR) of 25% would save 25,000 of them.

   To confidently show (say, P = 0.001) this moderate but important effect, you would need to enroll about 10,000 of these women. However, you already know that the sample sizes of most RCTs are in the dozens or hundreds. These trials are far too small to be able to detect relative risk reductions (RRRs) of 25% (or even 30% or 40%) when the control event rate (CER) is 0.10.. For example, Salim Yusuf and his colleagues reported that 21 of 24 trials of long-term beta blockade following myocardial infarction were too small to individually detect the 22% relative risk reduction (RRR) established in a subsequent meta-analysis. Returning to our example, a trial of only 500 women with coronary heart disease would be more than 90% likely to fail to show the efficacy of a treatment that reduced death by one-quarter. As a result, trials of promising treatments with important but only moderate effects (on important diseases) need to be really large.

2. For ultimately fatal diseases, preventing or delaying death provides a more convincing measure of efficacy than improving signs, symptoms, imaging, or laboratory tests. Death is simple, cheap, and unambiguous to determine. However, trials become complex and expensive when outcomes are signs (such as blood pressure in hypertension), symptoms (such as angina in coronary heart disease), diagnostic images (such as heart size in heart failure), or laboratory tests (such as tumor markers in cancer). This latter sort of trial is better suited for studying mechanisms than for determining efficacy. As a result, trials that use death as the measure of efficacy can have very simple follow-up and adjudication procedures.

3. For a treatment to be widely prescribed by busy clinicians to typical (i.e., not-very-compliant) patients, it has to be an easy regimen to prescribe, to follow, and to monitor. As a result, trials of practical treatments can have very simple interventions.

4. We should expect to observe differences in the degree of responsiveness of different patient subgroups to the experimental treatment (they called this a "quantitative interaction"). However, we should not expect to observe a difference in the direction of responsiveness, such that one subgroup would benefit from the treatment while another subgroup is totally unaffected or harmed by it (they called this a "qualitative interaction"). Moreover, if a trial is very large, even the subgroups that exhibit quantitative interactions should be equally distributed among the treatments. Two conclusions follow from this. First, really large trials needn't spend time and money on extensive baseline measurements. As a result, really large trials can have cheap, fast, and simple procedures for enrolling patients. Second, we are unlikely to improve the reliability of the

primary analysis for efficacy by identifying and statistically adjusting for such subgroups. As a result, really large trials can have simple analyses.

The first large, simple trial I know about was the 1954 trial of the Salk polio vaccine that recruited over 600,000 US schoolchildren[2]. However, nearly all trialists seem to have forgotten this strategy until reawakened by Salim Yusuf and his colleagues.

In the 20 years since their paper, trialists around the world have successfully carried out lots of large, simple trials. I think the classic modern example is ISIS-2. In it, they recruited 17,187 patients with suspected acute myocardial infractions in just xxx months[3]. They achieved a 19% relative risk reduction (RRR) in 2-year mortality by giving these patients aspirin plus streptokinase. ISIS-2's impact, both on clinical management and on the conduct of further large, simple trials, has been massive. Moreover, the conclusions of large simple trials have usually agreed closely with those of systematic reviews that combined enough small trials (frequently with indeterminate individual results) to assemble a comparably large number of patients.

However, in the eyes of most trialists and clinicians, one large, simple trial beats any meta-analysis of several small ones. For example, a meta-analysis of several trials on almost 4000 patients concluded that magnesium administration saved lives during myocardial infarction[4]. This conclusion was crushed by the large, simple ISIS-4 trial of 58,000 that concluded magnesium was worthless in this situation[5].

As you'll see in the Small Trials chunk that follows, large, simple trials are not necessary for many chronic, non-fatal disorders in which the goals of therapy are improvements in symptoms, function, or quality of life. Moreover, some trialists (especially in the US) argue that large, simple trials are just too simple to permit identification of mechanisms or of subgroups of patients at the extremes of risk and responsiveness. I've discussed this contentious issue on page xx.

The last 2 decades also have seen the laudable emergence of large, not-so-simple ("mega") trials. These trials have done more extensive baseline studies, applied more complex treatments, used more complex designs, and monitored for non-fatal events. A recent example is the HOPE factorial trial, also led by Salim Yusuf. It enrolled 9,297 patients who, for a variety of reasons, were at high risk of nonfatal and fatal cardiovascular events. Treating them with ramipril (an ACE-inhibitor) produced a 22% relative risk reduction (RRR) for myocardial infarction, stroke, or cardiovascular death[6]. Treating them with vitamin E was not effective[7].

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