Large trials – what have we learnt?

Doug Campbell
Auckland City Hospital

Introduction

Large randomised controlled trials (RCTs) in anaesthesia and perioperative medicine are a relatively recent phenomenon. In comparison, large trials in cardiology have been around since the early 1990s. The practice of cardiovascular medicine is now guided by large trials and megatrials in a way that anaesthesia and perioperative medicine is not. Large randomised controlled trials are part of the future of anaesthesia and perioperative medicine. This talk will focus on some of the important lessons from recent clinical trials, concentrating less on the detail of individual trials and more on the general principles of what we have learnt. Moreover, I will outline many areas of uncertainty about current practice that demand RCTs and how each of us can engage and contribute to these projects.

Efficacy, effectiveness and safety

Well designed, highly controlled trials can demonstrate efficacy. Often the real-world application of the treatment is difficult and diminishes the effectiveness of the intervention. That is why many large trials are pragmatic and test real-world application of the treatment (1). Similarly, if you are going to assess the benefits you have to look for harms. Many small trials do not even report on harms so any subsequent meta-analysis will be flawed. Large trials are necessary to weigh up the risks and benefits. These principles will be highlighted by the IHAST-2 and POISE-1 trials (2, 3).

Fragility

The P value is one way to evaluate the findings of a RCT. Low event rates in the primary and secondary outcomes in anaesthesia trials means the statistical significance of a trial result hinges on small changes in numbers of outcomes (4). The B-Aware trial is an example of a fragile result whereby one more case of awareness in the treatment group would have made the result non-significant (5). The trials Fragility Index is 1. Trials with a fragility Index of 3 or less are considered fragile. Very few anaesthesia and perioperative medicine trials are not fragile. Fragility Index can be easily described in binomial outcomes or time to event. However the principle that one or two outlying results in a continuous outcome could change the statistical significance extends the fragility concept in this group also. Worked examples will be demonstrated during the talk.

Equipoise and clinician (un)certainty

The principle of clinical equipoise is the ethical basis on which patients can be allocated to both arms of the trial as there is genuine uncertainty as to which is better. The purpose of the trial is to answer this question. Before all of the trials described in the talk I had a clear sense that one arm of the trial was more likely to be superior. I was often wrong, indeed, my ability to predict trial results is no better than chance! The Expert Opinion study polled 500 ANZCA fellows in Australia and New Zealand to predict the results of the ENIGMA-2 trial (7). Nitrous oxide has been in use for over 160 years, is a fundamental part of our practice, its physiological and pharmacological properties are part of the exam syllabus and there is a recent large trial, ENIGMA-1, to base our prediction on. The results of this survey will be used to highlight the point that we should all be less certain about what we know.

Endpoints

Choosing the correct endpoint for the primary and secondary outcomes of a study is a key design decision. Unfortunately, anaesthesia and perioperative medicine are awash with inappropriate endpoints. Moreover, inconsistent definitions often mean comparisons cannot be made between very similar trials in the field. A recent review of intraoperative hypotension found 130 relevant articles with 140 separate definitions of intraoperative hypotension (8). Surrogate endpoints are frequently used where the relationship between the surrogate and a meaningful enpoint is often unknown or not fully elucidated (9). The extrapolation from trials with surrogate endpoints has sometimes been catastrophic. Other specialities are trying to define relevant and consistent outcomes and this process will start in our speciality soon (10).

Future trial design

Advantages of factorial, step wedge and cluster randomised crossover trials will be discussed and why these might be the future of research in our speciality. Examples of each will be supplied with descriptions of their advantages and disadvantages. Where a trial is a comparison of two usual practice interventions then waiver of consent may be ethical.

This streamlining can allow a quick, efficient and cost-effective trial to be undertaken. Database research is often cited as cost-effective and can generate huge N. They are usually not definitive in their results.

How and why should I participate?

Research should be a core component of an individuals practice alongside teaching, audit and management. However, research is difficult without assistance and money. Participating in ANZCA trials group trials is a way of collaborating, seeking mentorship and generating income. Research nurses or assistants should be an integral part of most departments. I will outline a suggested business plan for departments interested in developing their departmental infrastructure (11).

dcampbell@adhb.govt.nz

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