The need for large and simple randomized trials in reproductive health

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Randomized trials are now well accepted as the most valid means of evaluating medical or surgical treatments, screening or preventive manoeuvres, as well as health, nutritional, social and educational interventions (1, 2, 3). Randomization is the only certain way of eliminating bias in how people are allocated to the treatment modalities being evaluated, and control for any known or unknown factors that may influence outcomes other than the treatments. There is a need for wider application of randomized controlled trial methodology to many important questions in reproductive health.

WHY DO WE NEED LARGE TRIALS?

In modern medicine, the best that can realistically be expected from most new treatments is a moderate effect. So we need to design studies that can discriminate reliably between differences in effects that are moderate but still have important clinical or programmatic value. These studies must guarantee strict control for selection bias by proper randomization (using sound design and appropriate statistical techniques), and strict control for the play of chance, which requires large numbers of participants (statistical power).

To assess moderate benefits reliably, we must be sure that biases and random errors have been avoided. This leads again to the need for large numbers of properly randomized patients who experience adequate number of events, which can be achieved by either large, simple randomized trials and/or by systematic reviews of randomized trials. Table 1. Why do we need large simple trials.

Table 1

Why do we need large simple trials
• To reduce, as much as possible, random errors
• To have the power to assess moderate effects
• To have the power to assess effects on rare conditions
• To have the power to assess effects in clinically important subgroups
• To have the power to demonstrate clinical equivalence
• To make it possible to do cluster randomization trials
• So that results are applicable to a wide range of people and settings

If the treatment effect is very large, there may be no need for randomized trials. Trials were not necessary when penicillin was first introduced, for example. However, for most, less dramatic, effective interventions aimed at most of today's priority diseases, it is unrealistic to expect such large effects on mortality or severe morbidity.

Some treatments do have large effects on other less substantive outcomes or on intermediate mechanisms of pathophysiology: drugs readily lower blood pressure during pregnancy, blood glucose can be controlled by diet or treatments, or tumour growth can be controlled temporarily by radiotherapy or chemotherapy. Although effects on these intermediate outcomes may initially appear to be important, effects on the more fundamental outcomes, such as mortality or severe morbidity are usually more modest. For example, hypertensive conditions in women with mild to moderate pregnancy-induced hypertension could be treated with anti-hypertensive drugs. There is, of course, good evidence that these drugs reduce blood pressure, but evidence from a recent systematic review failed to confirm their beneficial effects on other more substantive outcomes, such as pre-eclampsia, preterm birth or perinatal death, and some drugs even increase intrauterine growth restriction (4).

Reducing the potential for bias is equally important when evaluating complex health care interventions. For example, a large body of observational evidence, collected during the 1970s and 1980s, showed a strong inverse relationship between the number of antenatal care visits and the risk of having a low birthweight baby, or a perinatal death (5). Subsequent large randomized trials, in both developed and developing countries showed that the risk of low birthweight and perinatal mortality is similar for antenatal care programmes that have fewer visits compared to those that have the traditional number of visits (6).

WHY LARGE TRIALS NEED TO BE SIMPLE?

To recruit large numbers of people over a reasonable period of time, and at an affordable cost, large trials need to be simple. Complexity is a barrier to recruitment, interferes with clinical practice, encourages participants to leave the study early, and restricts generalisability of the results. If assessing eligibility is complex, or based on criteria not widely used in clinical practice, many eligible patients will not be randomized and the results will only apply to the relatively narrow group of patients recruited.

For rapid recruitment of large numbers of participants, eligibility criteria and the procedure for trial entry must be simple, so that they can be adapted and integrated into existing clinical practice. For example, screening for inclusion in the WHO Misoprostol Third Stage Trial (7), which recruited over 18,000 women in less than 3 years, included only four questions and there was no test or complex clinical examination. This trial recruited 65% of the screened pregnant women.

The Collaborative Eclampsia Trial (8), recruited 1687 women with eclampsia, by far the largest trial on this topic. Although in this trial, one factor in recruitment was the high prevalence of eclampsia in participating centres, equally important was that enrolling a woman in the trial made her clinical care easier than normal practice for the attending staff.

Furthermore, the intervention should be feasible to deliver within the existing health services. Data collection must be simple and based on information likely to be readily available in routine clinical notes. Information should only be collected if it is specified within the protocol as part of the planned analyses, and this should all be clinically relevant. No effort is then wasted collecting information that is unlikely ever to be used, or that has little clinical relevance. An additional advantage is that, in large trials, it is unnecessary to collect multiple baseline variables, because if randomization is correctly conducted and the treatment allocation adequately concealed, the baseline characteristics of treatment groups will be well balanced at trial entry. Only data for important prognostic variables need therefore be collected. As has been said before (4), usually it is of far greater value to collect 10 times less data on 10 times more patients.

SPECIAL SITUATIONS WHERE LARGE TRIALS ARE ALSO NEEDED

Demonstrating equivalence between treatments

New treatments are often advocated with the claim of equal effectiveness, but fewer or less severe side effects, easier mode of administration, or better cost effectiveness than standard therapy. Demonstrating clinical equivalence often requires larger sample sizes than for superiority trials. To demonstrate that any difference between treatment effects is clinically unimportant will require a larger sample size than demonstrating a difference that is clinically sufficiently large to be clinically important (9). Small trials tend to demonstrate that treatments are not different statistically, although there may be large clinical differences when sufficient numbers of participants accumulate in meta-analyses.

Cluster randomized trials

There is a growing interest in the use of cluster randomization or community trials. For most trials the unit of randomization is the individual person being allocated to a specific intervention or to a control or placebo. Other units (clusters) of randomization such as clinics, hospitals, physicians or families, can be used, and are particularly attractive for evaluation of health services (10, 11, 12). Advantages of cluster randomization trials are that they reduce "contamination" of the interventions between groups, they can increase participation, and they allow for better administrative and logistic organisation in implementing the intervention (10, 11, 12).

A disadvantage of cluster randomized trials is that they often need to be larger than a comparable trial based on individual randomization. If there is high homogeneity within each cluster, such as families or medical practices, the number of clusters within the trial will need to be large. It is always more advantageous to have large numbers of small clusters (i.e. clinics) than small numbers of very large clusters (i.e. cities) (13).

THE WAY FORWARD: GLOBAL PARTNERSHIPS

Often, to recruit sufficiently large numbers of people requires international collaboration (14). These international partnerships develop slowly, and are not without difficulties or cost. Developing a trial protocol with input from a diverse group of people requires searching for compromises with which everybody is comfortable, and that every centre is able and willing to follow. This may introduce

methodological difficulties, however. For example, in the WHO Antenatal Care Trial (15), which tested the hypothesis that a reduced number of antenatal visits is as effective as the more usual higher number of visits, there was concern that too flexible a protocol might actually bring the two interventions closer to each other, as had been the case in previous trials (6). Protocol flexibility needs to be a balance between allowing continuation of routine practices whilst maintaining methodological quality in trial procedures. Table 2. Some advantages of simple pragmatic trials.

Table 2

Some advantages of simple pragmatic trials

- Feasible to recruit large numbers of subjects
  - simple eligibility criteria
  - simple trial entry procedure
- Conducted within the existing health services.
  - intervention feasible without additional staff or technology
  - data collection based on information likely to be available in routine records
- Considerably less expensive than more complex studies
- Minimal additional work for already busy clinicians
- Encourages participants to stay in the trial
- More complete and better quality data
- Simpler data management
- Results relevant to clinical practice in a wide range of settings

Efficient communication between the trial coordinating centre and individual hospitals is crucial in order to resolve any problems without delay, and may present considerable challenges. Consent for participation in trials raises further issues, particularly as different countries will have different procedures and accepted norms. Most of these difficulties can be overcome through regular consultation that is sensitive to local norms, values and beliefs.

Partnerships based on mutual trust and respect are essential for the success of large collaborative trials. There is a growing demand for evidence from high quality large trials. International collaboration offers a feasible, enjoyable and productive route for addressing clinical questions of global importance. Although building these global partnerships is difficult and requires long term commitment, we believe the advantages outweigh the difficulties.

In conclusion, large trials are much needed to evaluate preventive strategies, treatments and health services (16). They are particularly important if the condition is rare (i.e. eclampsia, maternal mortality), the expected impact is moderate, equivalence between treatments is being tested, or the unit of randomization is a cluster rather than individuals.

Collaboration required for large trials among many research groups can be achieved in both developing and developed countries. All forms of care, whether drug or non-

drug, should be properly evaluated before being introduced into clinical practice. Large, simple, pragmatic trials play a central role in this scientific process. All of us can collaborate to make medical practice as scientific as possible for the benefit of our patients!

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