REVIEW

Randomised trials

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ABSTRACT

People involved in health care, either as providers or recipients, often need to make choices between different interventions, actions and strategies. They need evidence on the effects of the interventions and this should ideally come from systematic reviews of randomised trials. This paper describes three large, landmark trials from the last two decades, highlighting benefits to health and well being of this type of research. The International Subarachnoid Aneurysm Trial (ISAT) randomised patients with a subarachnoid haemorrhage to neurosurgical clipping versus endovascular coiling. It recruited 2143 patients and found a benefit of 24% for coiling in the primary outcome of death or dependency at one year, leading to substantial changes in practice and savings lives and resources. The MidU trial compared two different models of maternity care, midwifery- versus consultant-led care in north east Ireland. Pregnant women were only able to access the midwife-led units (MLUs) through the randomised trial. These were the first MLUs in Ireland and a total of 1653 women joined the study, which concluded that this form of care was as safe as consultant-led care, and associated with less intervention during labour and delivery. In the late 1990s, steroids were widely used in the treatment of patients with head injury. The CRASH trial was designed with a target sample size of 20,000 patients to detect reliably a reduction in mortality from 15% in the placebo group to 13% in the group allocated the steroid, methylprednisolone. However, it was stopped early when 10,000 patients had been randomised from 239 hospitals in 49 countries, and it was clear that corticosteroids did more harm than good. The analyses showed that 25.7% of patients allocated corticosteroids had died by six month compared to 22.3% in the placebo group (relative risk: 1.15, 1.07–1.24, p=0.0001). Randomised trials and, in particular, systematic reviews of randomised trials provide reliable and robust estimates of the relative effects of different interventions. They are key sources of information for evidence based health care and well–informed choices.

INTRODUCTION

People involved in healthcare, either as providers or recipients, often need to make choices between different interventions, actions and strategies. As well as considering factors such as feasibility, costs and preferences, these choices need to be informed by evidence on the relative effects of the different interventions on outcomes that matter to the people who will be affected by the decision.[1] This evidence should ideally come from systematic reviews of relevant research where the interventions of interest were compared in ways that isolate the effects of the interventions from other confounding variables by minimising the effects of chance and bias.[2] The most appropriate design for such studies is the randomised trial, in which the assignment of participants to the different options is done by a chance process: random allocation.

It is likely that several 100 000 randomised trials have been done. More than 600 000 reports are included in the world's largest single collection of such reports, The Cochrane Central Register of Controlled Trials (CENTRAL), in The Cochrane Library, and the number of reports is now growing by 25 000 or more every year.[3 4]

This article describes some large trials from the last two decades to illustrate key features of the design, conduct, analysis and interpretation of randomised trials. These landmark trials highlight the benefits to health and well-being of this type of research.

THE UNCERTAINTY PRINCIPLE AND THE TREATMENT OF SUBARACHNOID HAEMORRHAGE

The inclusion and exclusion criteria for a randomised trial determine who should, and should not, be recruited. They can be broad or narrow and will help to determine the applicability of the findings of the trial to other populations in different settings.[5] One of the ways to consider these eligibility criteria is in relation to the position of the trial on the spectrum from an explanatory (or efficacy) trial to a pragmatic (or effectiveness) study.[6] In the former, the researcher is seeking to recruit patients under close to ideal circumstances and might use tight well-defined eligibility criteria with strict diagnostic rules. In the latter, seeking to be closer to the world of practice, the researcher might set less stringent criteria and accept more typical means for diagnosing people with the condition of interest.

Examples of efficacy trials include randomised trials in which the pharmacokinetics of two formulations of a drug are compared in a laboratory setting with a small number of participants, all of whom are administered the relevant formulation under carefully controlled discussions. Such trials have narrow eligibility criteria to ensure that these people are as similar as possible. At the other end of the spectrum, one might compare prescriptions of different formulations of the drug in routine practice, seeking a wide range of people to reflect the variety encountered in practice and accepting that some participants will not take their allocated drug in the way intended.

In designing randomised trials so that they can be as large and widely applicable as possible, some researchers base their eligibility criteria on the 'uncertainty principle'.[7] Participants are eligible for such trials if they and the people recruiting them

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are sufficiently uncertain about the relative effects of the interventions for them. Where there is certainty about using one or other intervention (or about avoiding one), this certainty means that the person should not be recruited to the study. Such certainty might arise from patient preferences, contraindications or doubt about the safety of one of the interventions for the specific participant. The uncertainty principle reflects the dilemma faced in practice where two options are available and there is insufficient evidence to make a choice between them. In our daily lives this might lead one to flip a coin to decide. In a randomised trial, this random allocation is harnessed in order to capture new data that may resolve uncertainty in the future.[8]

One of several large trials to make good use of the uncertainty principle is the International Subarachnoid Aneurysm Trial (ISAT).[9 10] In this trial, patients with a subarachnoid haemorrhage due to a ruptured intracranial aneurysm were randomised to neurosurgical clipping versus endovascular coiling of the aneurysm. Patients for whom one of the treatments was clearly preferred or for whom one of the treatments was not suitable were not eligible for the study. Rather, patients for whom there was uncertainty about the potential benefits of the two treatments could be recruited. Over 8 years from the mid 1990s, 2143 patients were randomised using this uncertainty principle. It became the largest ever trial in subarachnoid haemorrhage and had sufficient statistical power to show a clear, but moderate, difference between the treatments.[11]

The primary outcome for ISAT was death or dependency at 1 year after randomisation, and a total of 576 (27%) of the randomised patients were known to have died or be dependent on the care of others at that point. There was a significant difference in this outcome between the two intervention groups: 326 (30.9%) of the clipping group were dead or dependent at 1 year compared with only 250 (23.5%) in the coiling group. This 24% relative benefit for coiling means that, for every 1000 patients treated by endovascular coiling rather than neurosurgical clipping, there were 74 more survivors who were not dependent after a year.[10] The use of the uncertainty principle maximised the number of eligible patients for ISAT and ensured that its result can be applied to future patients for whom either of the procedures would be acceptable. In the years since ISAT, audits of patients with subarachnoid haemorrhage in several countries including the UK and USA have shown a substantial increase in the use of coils and estimated that they had led to savings of both lives and resources.[12 13]

RANDOMISING FROM THE BEGINNING IN MATERNITY CARE

The researcher Thomas C Chalmers is often credited with the concept of 'randomise the first patient' as a means of ensuring that the evaluation of an intervention begins with the first patient.[14] The MidU study of maternity care in Ireland provides an example of the application of this idea.

MidU compared two different models of maternity care—midwife-led versus consultant-led care. The opportunity arose with the establishment of midwife-led units (MLUs) in north-east Ireland in 2004. These were the first MLUs in Ireland, arising from a 2001 report on women's health services in this region,[15] which emphasised the need for evidence-based care and recommended that MLUs be opened in the towns of Cavan and Drogheda in keeping with the findings of research from other parts of the world.[16] However, there was sufficient uncertainty about the applicability of this research to women in Ireland that policy makers responsible for maternity care, the North-Eastern Health Board (subsequently the Health Service Executive, Dublin North-East (HSE-DNE)), chose to introduce the MLUs within a randomised trial, MidU. The trial compared the effects of midwife-led care in a MLU with consultant-led care for healthy women without risk factors for labour and delivery. It set out to examine the effects on the use of interventions during pregnancy, labour and delivery; maternal satisfaction; neonatal and maternal outcomes; and costs. The aim was to assess whether midwife-led care delivered within the MLUs could be considered safe for an Irish population.

The trial began with a pilot phase in July 2004 to refine the eligibility criteria and practice guidelines. Recruitment to the main study took place between February 2005 and November 2006 in accordance with the sample size calculation, and the last baby was born in June 2007. The trial used a 2:1 randomisation ratio to make best use of the resources available in the MLUs, and the MLUs were only available to women who were randomised to this form of care within MidU. A total of 1653 women were randomised and the principal analysis of the trial focused on nine neonatal and maternal outcomes. These analyses led to the conclusion that the form of midwife-led care used in MidU was as safe as consultant-led care and associated with less intervention during labour and delivery. For example, there were no statistically significant differences between the two forms of maternity care in caesarean birth, induction, episiotomy, instrumental birth, low (ie, <8) Apgar scores or postpartum haemorrhage. MLU women were significantly less likely to have continuous electronic fetal monitoring or augmentation of labour. Breastfeeding initiation was similar between the two groups of women, showing no benefit of midwife-led care.[17]

NOT EVERYTHING WORKS—STEROIDS AND HEAD INJURY

A recent Cochrane Methodology Review found that experimental treatments tested in randomised trials are on average only slightly more likely to be beneficial than existing treatments, at least in the context of publicly funded trials.[8] This supports our continuing reliance on the aforementioned uncertainty principle to identify eligible patients and the ethical justification for randomised trials. It shows that the probability of benefit is similar and unpredictable between the treatments, and that we should expect that using an intervention will sometimes be found to be worse than avoiding it when tested in an adequately powered randomised trial.

In the late 1990s, following decades of use and with some supporting evidence from randomised trials that had recruited hundreds of patients, steroids were widely used in the treatment of patients with head injury. The hope was that the treatment would improve the survival of the millions of people who suffer a head injury each year. In 1997, a systematic review suggested that the size of the benefit might be small, perhaps an improvement of only a few percentage points on mortality.[18] Amidst this uncertainty about the size of the effect and the possibility that steroids might not have an effect on survival, it was recognised that a large randomised trial would be needed to confirm or refute a small survival benefit for steroids.

The CRASH trial was designed with a target sample size of 20 000 patients, which would be enough to detect reliably a reduction in mortality from 15% in the placebo group to 13% in the group allocated the steroid methylprednisolone. The first patient entered the study in April 1999 and, over the next 5 years, approximately 10 000 patients were randomised from 239 hospitals in 49 countries. The trial was stopped at this point, in May 2004, following advice from the Data Monitoring and Ethics Committee (DMEC) to the Trial Steering Committee. The DMEC recommended that the trial be stopped because, rather than a small or moderate benefit for steroids, they had detected that

patients were more likely to die if allocated to this treatment rather than control. In the preliminary analysis published in the *Lancet* in October 2004, the risk of death from all causes within 2 weeks of treatment was 21.1% in the group allocated corticosteroids compared with 17.9% in the placebo group (relative risk 1.18, 95% CI 1.09 to 1.27, p=0.0001).[19]

The following year, when the analyses of the 6-month mortality for 9673 (96.7%) of the 10 008 patients who were randomised into CRASH were available, the risk of death at this time point was found to be higher in the corticosteroid group than in the placebo group. There had been 1248 deaths in the former and 1075 in the latter, indicating that 25.7% of patients in the steroid group had died by 6 months compared with 22.3% in the placebo group (relative risk 1.15, 95% CI 1.07 to 1.24, p=0.0001). The authors reported that these updated results supported their conclusions in the earlier paper and the decision to stop the trial, suggesting that corticosteroids should not be used routinely in the treatment of head injury.[20]

CONCLUSIONS

Throughout most of medical history, personal experience, case histories and non-randomised comparisons of patients treated in different ways dominated the evidence base for choices between interventions. Although these sources of knowledge remain in use today and can provide useful information for practitioners, patients, policy makers and the public, the risk of bias within them makes their use in determining the relative effects of treatments on important outcomes potentially unreliable. In the second half of the 20th century and now into the 21st century, the role of randomised trials—and in particular systematic reviews of randomised trials—as sources of reliable and robust estimates of the relative effects of different interventions has become widely accepted.[21 22] This article describes three examples of randomised trials that have had important impacts on practice, providing background on why these studies were done and how they generated findings that helped resolve important uncertainties in healthcare.

Competing interests None.

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REFERENCES

1 Williamson P, Altman D, Blazeby J, *et al*. Driving up the quality and relevance of research through the use of agreed core outcomes. *J Health Serv Res Policy* 2012;17:1–2.
2 Antes G, Clarke M. Knowledge as a key resource for health challenges. *Lancet* 2012;379:195–6.
3 Ghersi D, Pang T. From Mexico to Mali: four years in the history of clinical trial registration. *J Evid Based Med* 2009;2:1–7.
4 Bastian H, Glasziou P, Chalmers I. Seventy-five trials and eleven systematic reviews a day: how will we ever keep up? *PLoS Med* 2010;7:e1000326.
5 Yusuf S, Held P, Teo KK, *et al*. Selection of patients for randomized controlled trials: implications of wide or narrow eligibility criteria. *Stat Med* 1990;9:73–86.
6 Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis* 1967;20:637–45.
7 Peto R, Baigent C. Trials: the next 50 years. Large scale randomised evidence of moderate benefits. *BMJ* 1998;317:1170–1.
8 Djulbegovic B, Kumar A, Glasziou PP, *et al*. New treatments compared to established treatments in randomized trials. *Cochrane Database Syst Rev* 2012;(10): MR000024.
9 Molyneux A, Kerr R, Stratton I, *et al*. International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* 2002;360:1267–74.
10 International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* 2005;366:809–17.
11 van der Schaaf I, Algra A, Wermer M, *et al*. Endovascular coiling versus neurosurgical clipping for patients with aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev* 2005;(4):CD003085.
12 Gnanalingham KK, Apostolopoulos V, Barazi S, *et al*. The impact of the International Subarachnoid Aneurysm Trial (ISAT) on the management of aneurysmal subarachnoid haemorrhage in a neurosurgical unit in the UK. *Clin Neurol Neurosurg* 2006;108:117–23.
13 Qureshi AI, Vazquez G, Tariq N, *et al*. Impact of International Subarachnoid Aneurysm Trial results on treatment of ruptured intracranial aneurysms in the United States. *J Neurosurg* 2011;114:834–41.
14 Chalmers TC. Randomize the first patient. *N Engl J Med* 1977;296:107.
15 Kinder P. *Report of the Maternity Services Review Group*. Kells: North Eastern Health Board, 2001.
16 Hatem M, Sandall J, Devane D, *et al*. Midwife-led versus other models of care for childbearing women. *Cochrane Database Syst Rev* 2008;(4):CD004667.
17 Begley C, Devane D, Clarke M, *et al*. Comparison of midwife-led and consultant-led care of healthy women at low risk of childbirth complications in the Republic of Ireland: a randomised trial. *BMC Pregnancy Childbirth* 2011;11:85.
18 Alderson P, Roberts I. Corticosteroids in acute traumatic brain injury: a systematic review of randomised trials. *BMJ* 1997;314:1855–9.
19 CRASH trial collaborators. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet* 2004;364:1321–8.
20 CRASH Trial Collaborators. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet* 2005;365:1957–9.
21 Clarke M. Doing new research? Don't forget the old: nobody should do a trial without reviewing what is known. *PLoS Med* 2004;1:100–2.
22 Clarke M, Hopewell S, Chalmers I. Clinical trials should begin and end with systematic reviews of relevant evidence: 12 years and waiting. *Lancet* 2010;376:20–1.