reviews

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Randomised Controlled Trials: A User's Guide

Alejandro R Jadad

BMJ Books, £12.95, pp 152
ISBN 0 7279 1208 9

Rating: ★★★

The book's subtitle sets the tone. Born of the author's struggle to find, understand, interpret, and use randomised controlled trials, this book is the fruit of years of jotting down questions and searching (often in vain) for answers. It is a concise but complete guide to randomised controlled trials, intended for the long list of their potential users.

Jadad leads us through the basics of randomised controlled trials, the sources of bias at all stages, the tools for assessing the quality of trials, the essentials of reporting and interpreting them, and how they fit into the overall picture of information used to make decisions. Using as a template the CONSORT statement, developed to improve the quality of reporting of trials, the author describes the essentials that users need to consider in interpreting trial results.

Particularly refreshing is the author's clear exposure of the pitfalls of randomised controlled trials and his warnings to those overzealous converts to the doctrine of evidence based medicine who would put their total faith in nothing but randomised controlled trials. As a leader in the field of analysing, studying, and using such trials, Jadad, in simple and forceful language, brings home the absolute necessity of randomised controlled trials for rational decision making. Yet he also convincingly demonstrates their limits and the barriers to their effective use and describes other sources of information that must be taken into account when making healthcare decisions.

Breaking the book into short and easily digestible chapters makes it all the more user friendly, as does the author's informal style of writing. Jadad's book is unique. A visit to the library and a search on the internet of the "Earth's biggest bookstore" revealed only titles that were at least twice the volume, and twice the price. None address the specific needs of users of randomised controlled trials as Jadad's book does.

This is not to say that "doers" will not find ample matter for reflection. Quite to the contrary. All are well served by the author's successful resistance of the temptation to write a general book about randomised controlled trials. As it is, the list of current, would be, and should be users of controlled trials is so inclusive that I am not sure the book will meet the needs of all of them. At present, the main users of randomised controlled trials are busy clinicians trying to practice evidence based health care and those developing guidelines to assist them. They will benefit most from the book. I hope that patients, their relatives, politicians, and healthcare financing agencies will also come to lean on this enjoyable and thought provoking book.

John-Paul Vader, *senior physician researcher, Healthcare Evaluation Unit, Institut de Médecine Sociale et Préventive, University of Lausanne, Switzerland*

JOURNALS

Choosing between randomised and non-randomised studies: a systematic review

A Britton, M McKee, N Black, K McPherson, C Sanderson, C Bain

Health Technology Assessment
1998;2(13):pp 214

Rating: ★★★

Randomised controlled trials are often held up as the "gold standard" of medical research, and it is commonly believed that the size of a treatment effect is exaggerated in non-randomised studies. In these days of evidence based medicine, however, where is the empirical evidence that this is so? A widespread criticism of randomised controlled trials is that they are based on highly selected individuals. Are there systematic differences between patients included and excluded in such trials, and do these influence the measured treatment effect?

These are just a few of the questions that Britton and colleagues have attempted to address in their review. The other questions they consider are to what extent it is possible to adjust for baseline differences between study groups, and how important is patients' preferences in terms of outcome. The answers to these questions inevitably depend on the quality of the available evidence. The authors found 18 papers comparing randomised controlled trials and prospective non-randomised studies with the same intervention and similar settings and found no consistent pattern in the effect size. They give a variety of reasons both for a larger effect and for a smaller effect in randomised controlled trials. For example, higher quality interventions in randomised controlled trials may produce a larger effect, and the fact that non-randomised studies may contain a disproportionate number of patients with a greater capacity to benefit (in one arm) may produce a smaller effect. Four separate chapters consider case studies in surgical interventions, drug interventions, organisational interventions, and preventive interventions.

The answers to the other questions posed by the authors are more vague. As one might expect, there are differences in patients included in treatment trials and those included in prevention trials: patients in the latter are more affluent, better educated, and more likely to adopt a healthy lifestyle, although evidence is limited because few studies report details of the non-participants. Britton and colleagues conclude that adjusting for differences in baseline prognostic factors often changed the estimated treatment effect, but not "significantly" and not consistently. There were only four studies that directly examined the effects of patients' preferences on treatment estimates, and there was some suggestion that preferences could account for some of the differences between randomised controlled trials and non randomised studies.

Britton and colleagues conclude with some recommendations for more representative, pragmatic trials, and for better reporting of characteristics of eligible patients who did not participate. Overall this is a useful review, and if the authors did not answer all the questions they set themselves at the outset, they have at least demonstrated that the reason for this apparent failure is that the evidence is not available yet and map out useful areas for future research.

M J Campbell, *professor of medical statistics, University of Sheffield*

CD roms

Urinary Disorders and Male Health: A Decision Making Guide for Patients

Royal College of Surgeons, British Association of Urological Surgeons, Merck Sharp and Dohme, free to clinicians and public information organisations

Rating: ★★ for patient value, ★★★ for doctor value

With information technology now commonplace, it was inevitable that such technology should reach patients' waiting areas. With the increasing awareness of health issues, patients expecting or demanding detailed insight into their health or disorder, and anything to do with health occupying prime time television, what could be more appropriate in a waiting area than an interactive CD player providing medical information? The difficulty is standardisation.

Patients are individuals and can bring to their consultation a host of psychosocial variables that are not evident until explored. Patients are of varying intellectual ability and live and work in different environments and cultures. Doctors, too, are individuals. Even with shared care programmes, protocol management, evidence based medicine, and clinical audit, they are still individuals with individual thoughts, ideas, and plans. The rapidly changing face of medicine, the increasing range of drugs, surgical techniques, and non-invasive procedures do little to improve our ability to standardise care.

It becomes frighteningly difficult then to design an information CD, suitable for inclusion into any patient waiting room, that will suit all needs. *Urinary Disorders and Male Health* attempts to provide information on urinary symptoms, from prostatitis to prostatic cancer, from infections to bladder tumours. Designed exclusively for male patients, it aims to fill in the gaps that the doctor forgot or was too busy to tell. A real need.

With extremely effective graphics and soothing background music, it makes the mistake of trying to tell everything. It moves comfortably from very basic anatomy to complex staging of bladder cancers, from the aetiology of bladder tumours to microwave therapy for benign prostatic hypertrophy. Unfortunately, it assumes that its audience is conversant with medical terminology and freely uses words such as hyperplasia, transitional cells, and carcinoma in situ.

The need for information if you are about to undergo a total cystectomy is not in dispute, and the CD handles this well. However, a patient asking you for a Mitrofanoff procedure may not be expected.

All is not lost, however. Despite its limitations, this CD will be of use to doctors. Its thoughtful and up to date presentation of the diagnosis and management of urinary problems will provide general practitioners and junior hospital doctors with the answers to all those difficult questions that patients ask after seeing the consultant or, more commonly, after seeing a television programme the night before.

Trevor Gibbs, *director, Community Studies Unit, Department of Primary Care, University of Liverpool*

@ www

WEBSITE OF THE WEEK

www.current-controlled-trials.com This week's site does not exist. Well, the one I was tipped to review is "vapourware," software implemented only in the mind of its progenitors. It seems the world will have to wait a little longer for the mega-archive of all randomised controlled trials being compiled by the ad hoc group for controlled trial registration.

No matter, a search engine makes it possible to start from nowhere. My favourite this past six months has been Ask Jeeves (http://www.askjeeves.com), which accepts natural language questions and resubmits them to the important search engines. This approach will find randomised controlled trials (at random), but it does also find one important methodological piece. Full marks to the editors of *JAMA* for getting its CONSORT guidelines to be Infoseek's number one pick (http://www.ama-assn.org/sci-pubs/journals/archive/jama/vol_276/no_8/ed6043x .htm). This is done by using metatags, non-printing information at the top of each web page recognised by the search engine.

Alternatively, you could trust an expert. Andrews Booth's Netting the Evidence (http://www.shef.ac.uk/uni/academic/R-Z/scharr/ir/netting.html) is a good introduction to the world of evidence based health care. Mr Booth surrounds evaluated links with pithy description, which helps avoid the hyperplunge to irrelevance. It is ironic that you are more likely to meet a textbook-style summary than a randomised controlled trial in evidence based health care these days.

Douglas Carnall
BMJ

BOOKCASE

● Dick-Read's **Natural Childbirth** was published in 1933. Its plangent criticism of current obstetric practices made the author few friends among the "O&G" establishment. But many women saw his contribution to the reshaping of medical attitudes to childbirth differently. In **Post-war Mothers. Childbirth Letters to Grantly Dick-Read, 1946-1956** (University of Rochester Press, £35, ISBN 1 878822 87) Mary Thomas has collected letters he received from anxious women and his invariably courteous responses.

● We hear a lot about obesity, leptin, and neuropeptide Y but not much about the process of ingestion of food. **The Scientific Basis of Eating** (Karger, $190.50, ISBN 3 8055 6498 8), volume 9 in the grandiloquently named series *Frontiers of Oral Biology*, is about how we smell and taste, chew, and swallow and the way in which these activities are integrated by the nervous system. It's really for the specialist, but many will be interested in Edmund Rolls' chapter about gustatory and olfactory processing in the brain and the control of eating. The concept that there are only four prototypical tastes—sweet, sour, salty, and bitter—is under attack. It seems that there are separate cortical representations of at least two other taste qualities—umami, the flavour of monosodium glutamate that is present in proteins from various sources, and tannin, the astringent taste found in a large range of spices, wines, and, of course, tea.

● Disabled people and those who advise them will find **Furniture** (The Disability Information Trust, £10.00, ISBN 1 873773 15 3) invaluable. It's an illustrated catalogue of beds, chairs, tables, and other equipment specially made for people with disability. Not only does it provide detailed information on the equipment that is available, it also gives advice on where and how to get it.

● Murphy's law states that if anything can go wrong it will. To minimise the effects of this law, the pharmaceutical industry uses standard operating procedures, defined as detailed written instructions to achieve uniformity of the performance of a specific function, in the conduct and reporting of clinical trials. **Good Clinical Practice. Standard Operating Procedures for Clinical Researchers** (John Wiley, £29.95, ISBN 0 471 96936 2) is a compilation of checklists. Anyone concerned with clinical research, especially trials of drugs and medical devices, might find that it saves them a lot of time.

● The level of medical and anatomical knowledge of the ancient Greeks was unsurpassed in Western culture until the 16th century. In **Greek medicine. From the Heroic to the Hellenistic Age. A Source Book** (Duckworth, £14.95, ISBN 0 7156 2771 6) James Longrigg provides a selection and translation of some of the most interesting classical texts.

Christopher Martyn, BMJ

PERSONAL VIEWS

Tuberculosis: story of medical failure

Western medicine's conceit is such that most doctors remember streptomycin only for giving birth to randomised controlled trials. They have a far clearer recall of the wider intellectual revolution it spawned than of the disease originally targeted.

The streptomycin trial was the first of many conducted by the British Medical Research Council (MRC) to engineer effective chemotherapy for tuberculosis. Failure to implement the resultant standardised regimens has led to an international resurgence of tuberculosis. Despite the effective treatment developed nearly 50 years ago, tuberculosis now kills more people than ever.

This should trigger some questions from the public, which funds all medical research. For example, why, after an estimated one million controlled trials on every treatment under the sun, have we failed to apply the results of the initial ones on tuberculosis chemotherapy? Why do so many countries still lack basic drugs and microscopes, and why is the principal curative distillation of all this effort still available to only one in six patients with tuberculosis throughout the world?

Tuberculosis certainly had a higher priority in 1948. The MRC owes its existence to public clamour over the disease. Tuberculosis was also responsible for Austin Bradford Hill's career switch from medicine to statistics.

The success of the streptomycin trial spawned a string of others by the MRC's tuberculosis research unit. The unit's overseas collaborations showed how rigorous science could be specifically modelled to meet the needs of individual developing countries in order to provide affordable and effective treatment. Its work remains a paragon which has yet to emulated.

A trial in India showed that people in the worst possible conditions could be cured just as well at home as in hospitals. At a stroke the entire purpose of sanatoriums disappeared, wiping billions of dollars off European and North American healthcare budgets. The Swiss resort of Davos reinvented itself as a meeting place for the finance ministers of the world's richest nations.

But in the colonial expansion of the last century European emigrants were primary exporters of tubercle bacilli. Tuberculosis killed more native Americans than the Seventh Cavalry. In return for gold and diamonds, native mine workers in Southern Africa were exposed to bacilli coughed up, if not by Cecil Rhodes then certainly by many of his friends. The MRC's extensive studies in East Africa formed the basis of later work in Tanzania which ultimately provided the current DOTS (directly observed treatment, short course) strategy.

Mainstream Western medicine seized on the idea of randomised trials while simultaneously expunging tuberculosis from its consciousness. It disappeared from medical school curriculums as quickly as it did from the research programmes of pharmaceutical companies and the political agenda.

By 1986 the MRC unit had been disbanded by Mrs Thatcher's government, a result of what some saw as her disdain for altruistic foreign aid. Such indifference was reflected at the World Health Organisation. Tuberculosis scarcely figured in its publications during the late 1980s and by the end of the decade its entire tuberculosis monitoring and control operation had been reduced to one person.

This complacency was ruthlessly exposed by the advent of HIV, which allowed dormant tuberculosis to reactivate. A string of extraordinary events followed in the 1990s when the affluent world woke up to the fact that it was still at risk of a disease which does not recognise any geographical, social, or racial boundaries.

> We had the chance to control this disease and we blew it

New York City had to look to Tanzania to find out how to control its own explosion in tuberculosis. In 1993, a reinvigorated WHO took the unprecedented step of declaring tuberculosis a global emergency and has since made intensive efforts, backed by the World Bank, to tackle the epidemic.

We had the chance to control this disease and we blew it. The easy option is to blame politicians and the media and revert to standard pessimism that nothing can be done in the face of the complexities and cost of curing people of tuberculosis and the ever rising economic gulf between rich and poor nations.

But this should not be used as a fig leaf for medicine's failings. Ironically, the first half of this century saw unprecedented press and political interest in tuberculosis when all medicine came up with was quackery. When medicine was able to offer the prospect of cure honed on the anvil of science, the silence from the rest of us was deafening.

The MRC studies highlighted from the outset the dangers of emerging drug resistance and devoted considerable energy to developing treatments to minimise poor patient compliance. The failure of doctors to follow established protocols and proved regimens is well documented in both rich and poor countries.

YACOV ECKEL

Franz Kafka accused medicine of "hunting a beast through endless forests"

Trials undoubtedly have a place in shaping medical practice, but patients do not get better on confidence intervals. Evidence based medicine can never work if a significant minority of doctors deem it inadmissible at the outset. Mainstream medicine in affluent countries chose to weave its entire epistemological framework around the concept of controlled trials. Doctors need them to further their careers and fill an estimated 22 000 biomedical journals around the world. In the process they have spawned a monster of uncontrolled research which is impossible to digest and apply in practice.

Something has got lost along the way in the quest for the holy grail of therapeutic paradigm: a wider sense of purpose and reality. Franz Kafka may have predicted it before succumbing to tuberculosis when he equated medicine blindly chasing cure as though "hunting a beast through endless forests."

Maybe he was right. It is something the leaders of the world's richest nations might chew over when they next pig out at Davos. For a disease caused by inspiration, there is plenty of room for inspirational leadership. But don't hold your breath.

Chris Holme, *Herald newspaper, Glasgow*

If you would like to submit a personal view please send no more than 900 words to the Editor, BMJ, BMA House, Tavistock Square, London WC1H 9JR or e-mail **editor@bmj.com**

Evaluating new treatments

Fifty years ago medicine entered a new phase in evaluating new medical treatments in the form of randomised clinical trials, with control patients often given placebos. At the same time there was a widely accepted view that retrospective controls were "inherently fallacious." But 20 years ago, this argument was challenged in the *BMJ*, and retrospective controls were advanced as an alternative to randomisation.

It was recognised that the advent of modern computer technology made more practical the use of retrospective controls by facilitating the storage and retrieval of detailed medical data on past cases, and in comparing past with current medical experience. The *BMJ* endorsed this view. But the intervening 20 years have seen little change in practice. Today, randomised clinical trials with placebos are, with few exceptions, the prevailing method of evaluating new treatments. Yet alternatives surely warrant more attention than they have received—in particular, what is now usefully called a "computrial."

Alternatives surely warrant more attention than they have received

A computrial is one which admits all suitable patients to the same experimental treatment, while controls are drawn from the records of patients who have received treatment in historically recognised, leading treatment centres, not just random treatments. Controls are matched individually by computer with appropriate software to the trial patients for all significant prognostic factors. A computrial generates not just statistical summary data on the collective response to the new treatment. It creates a record which can be cross analysed for the effects of particular prognostic factors, with implications for individual patient treatment, and it compares a new treatment with the best of the old. It eliminates placebos and the deterring uncertainty that faces every patient in a randomised trial as to whether he or she is receiving the newest treatment or is being relegated to the passive role of a control.

The computrial concept claims respectable origins. In 1965 the late Sir Austin Bradford Hill, in his famous Heberden Oration, *Reflections on the Controlled Trial*, expressed reservations about the indiscriminate use of randomised trials, and discussed in favourable terms the use of retrospective controls based on patient histories instead. On 19 November 1979 the *BMJ* published my paper, repeatedly rejected since 1972, "Do retrospective controls make clinical trials 'inherently fallacious'?" which challenged the then accepted view.

Debate started with a concurrent editorial, "Randomised controlled trials?" that endorsed my views, citing the power of computers to match trial patients with historical controls, and concluded with these words: "The controlled trial has been placed on too high a pedestal and needs to be brought back to earth." Some readers wrote in support; others were opposed. The debate ended six months later with my rejoinder to critics.

With such a send off from the editors of *BMJ*, computer enabled clinical trials with retrospective controls should soon have had their day, at least on an experimental basis, particularly with the explosive growth in numbers and power of computers. This has not been the case, however, despite many strong criticisms of randomised trials over the years.

Heartened by the response to my 1979 publication, I have repeatedly encouraged use of what I now call computrials, but the effort has been unproductive even though the original concept has been expanded to include use of computers to particularise treatment to individual patients rather than provide statistical results only, and emphasis is placed on controls that have received the best treatment medicine had to offer before the new treatment appeared. The most recent experience with one of the world's leading pharmaceutical companies is worth recording because it has lessons for medical innovators generally. Its essential result was a refusal to engage in discussions among colleagues, and a summary rejection of the written, fully documented proposal, with no reasons given.

The ethical and management issues raised in the encounter just described with the technical staff of a world famous pharmaceutical company may be as important as the ethical issues involved in randomised clinical trials themselves. If there is no dialogue among colleagues on matters that affect the evaluation and use of a company's innovative products how can you assume that issues raised have been dealt with in good faith, and that serious concerns of cost, efficacy, and ethical propriety are not being buried to conceal excessive costs and ethical shortcomings of current practices, or that official favour is being curried at the expense of scientific advance?

A colleague takes the view that only legislation that relieves the United States Food and Drug Administration of responsibility for evaluating the efficacy of drugs will improve the present situation. My own view is that the FDA is a responsible agency, and that it will in due course accept a less theoretically rigid and more empirical policy towards evaluating new drugs and other treatments if the medical and scientific community says it should.

I would like to thank Professor Emil J Freireich for his useful comments.

Lawrence Cranberg, *consulting physicist, Austin, Texas, USA*

SOUNDINGS

Winter draws on

Years ago a snowy haired anatomy lecturer used to make us cringe with his double entendres. Smutty jokes can be funny if they have a touch of wit but once they lose their freshness they are just embarrassing, even to preclinical students.

That sad old man is gone now but his spirit lives on in the British advertising industry. The latest blitz from behind the admen's bicycle sheds is promoting brown bread, of all things. "Butter me up and I'll go down a treat," said a poster as I drove to work. As I was supposed to, I felt guilty for imagining sexual undertones but further on the message was more explicit: "Let's play hide the sausage."

Our city centres now have wall to wall urological innuendo. Billboards promoting a television show tempted us with "Cox out in Greece." In the Renault advertisements, Papa and Nicole have given way to: "Size matters. It's what you do with it that counts." Cigarettes are "longer than John's." And of course French Connection UK has its initials everywhere.

If a poster shows a nipple there is an outcry but these slogans are like Rorschach blots. Some people see nothing in them, and the rest of us keep quiet for fear of being accused of seeing sex everywhere. We remember the ridicule heaped on the BBC's old *Blue Book*, which cited "winter draws on" as the type of joke that could give radio a bad name.

I like saucy British humour, in its place. Every time I see a chihuahua I remember Max Miller. I sit happily through the dregs of the *Carry On* series on late night television. But the art of innuendo lies in knowing how far to go, and I think bus shelters full of schoolchildren are a nudge too far.

The young provide an easy excuse for my indignation. The girls in my clinic with unwanted pregnancies are little older than those tittering at the posters, and every week I become more exasperated at the British way of treating sex with fourth form sniggers rather than education.

But really, I just don't like tat in public places. Do we need billboards at all—even those in good taste? They are ugly, a hazard to road safety, and commercially unnecessary in our television age. Get them down, if you'll pardon the expression.

James Owen Drife, *professor of obstetrics and gynaecology, Leeds*