Randomized Controlled Trials

Questions, Answers, and Musings

Second edition

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We dedicate this book to the memory of our exemplars:
Titus Lucretius Carus (Lucretius) (99-55 BCE)
Sir Austin Bradford Hill (1897–1991)
Who live on in the precedents they set.

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Contents

Foreword

I first met Alex Jadad at "Closing the Loop", an international conference on evidence-based practice, in 1999. His talk was a lively and amusing journey through the perils and pitfalls of the world of randomized controlled trials (RCTs). Afterwards we found an immediate sympathy with each others' views. We both recognized the value of research and also the various conundrums that arose in the interface between research and practice. We also felt that there were issues we could pursue together. We exchanged books and papers and wondered what we could do next.

When I received it, the first edition of *Randomised Controlled Trials* was an eye opener for me. Its painstaking overview of the design, understanding and application of RCTs enumerated many of the pitfalls, possible biases, and faulty designs inherent in the process, while at the same time recognizing the potential importance of finding genuine evidence for improved practice. It made an explicit promise that there would be more to come.

My discussions with Alex centred on what we recognized as an implicit assumption in the book. It seemed to be saying that "if only" we could rid ourselves of our biases, if we could only be more careful about the random allocation, if only we could perfect the way we carry out and report our experiments, then we could come up with the appropriate and rational answers to our clinical questions.

It was this implicit assumption that we began to question. It maintained that the problem was in the methodology of clinical research, rather than in the nature of the world of health and illness. It presumed that underlying the apparent mess there was a deeper order that could be discovered through rigorous research, that an understanding of this deeper order would in turn provide us with appropriate clinical protocols. We felt that it was worth thinking about the possibility that the world of health and illness might not be as orderly as we had assumed. Although large areas of pathophysiology and many diseases lent themselves to this rational deterministic model, there might also be many clinical circumstances where the model might not apply.

In philosophical terms we could say that the issue might be *ontological* rather than *epistemological*: about the *nature* of reality rather than about *how* we know it. For Alex it was a problem related to the realities of medical practice – how health professionals interacted with patients and how various factors influenced the interventions they made. Alex often spoke about his father, who was a particularly talented GP in South America. Alex thought of him as a model practitioner. His gift for understanding the needs of his patients and long experience in the use of a very limited number of drugs resulted in a noteworthy success in keeping his patients healthy.

Alex introduced me to Murray Enkin, his co-author for this second edition. Murray was an obstetrician who combined the experience of a sensitive caring practitioner, like Alex's father, with a strong commitment to providing a basis of evidence for good practice. They had met in Oxford where they had both been deeply involved in the evidence-based movement. The three of us, with like-minded colleagues, later initiated the Clinamen Collaboration to explore other models for thinking about health and health care.

We found the distinction between "simple" "complicated" and "complex" useful in our discussions. Where the problem is simple, there are often pre-tested solutions that are universally applicable – something like recipes for baking a cake, or straightforward clinical protocols that had few exceptions. Much medical practice is like this. It is scientifically based, well tested and lends itself to straightforward replicable recipes, and provides a firm basis for treating simple infections, inflammations, cuts and bruises.

More intricate problems are similarly solvable, but may require more complicated protocols. They need many more "recipes" strung together, and more technical expertise. Kidney transplant surgery, for example, requires a highly skilled surgeon, whose expertise will improve with experience. It also requires teamwork with other disciplines, varied but replicable facilities and resources. With each repetition the process is refined, understanding is increased, and results become more predictable.

Complex problems, like chronic illnesses and multi-system disease, are entirely different. They are not standardizable, but rather depend more on each individual case and context. The example of raising a second child is often used to make this point. Although some formulae fit all children, many do not. The approaches that worked for one's first child are only occasionally applicable to

the second. Similarly, results of clinical interventions for complex problems may be impossible to predict. Few patients are alike, and even the same patient can respond differently at different times. Research is useful and instructive, but is not a substitute for clinical sensitivity to the unique situation of each individual patient.

This second edition takes into account the complexity of some areas of health care. Although it continues to recognize the importance of more stringent procedures and better experimental design, it now acknowledges that these will not be sufficient to solve the problems associated with the use of RCTs in practice. The musings added to each chapter explore what might be further needed to change the nature of the research enterprise, to allow a wider and richer source of evidence in the interplay between patients, research results and medical interventions.

Just as the first edition of this book was ground-breaking during the beginnings of evidence-based practice, this edition suggests many new possibilities and approaches to improved research for practice. From my perspective, I see several places where Jadad and Enkin begin to explore these issues.

In the case of chronic care, the role of the patient is especially important in searching for ongoing ways of coping with and treating a constellation of illnesses. The things that help are often discovered by patients and their families. Only they, not health professionals, can tell from their experience how and when foods are best taken, how hands-on care is properly applied, the subtle side effects of various medications and ways to avoid them. This is not merely to democratize medicine, but to recognize that useful interventions can be gathered from the kind of self-care that is part and parcel of chronic disease management. Increasingly useful self-help groups associated with various conditions pass on useful information of this kind. Experimental validation of these "tips" requires a different kind of attention and special methods.

In the current state of the health system, with its great emphasis on instrumental diagnosis, measurable and replicable results, the fact that not every aspect of care is susceptible to quantitative evidence can lead to scepticism about the entire enterprise. The widespread belief that if we can't measure it, it does not exist can lead to a sense of nihilism: This is clearly not warranted.

Let me go back to the example of raising a second child. The fact that there are not clear protocols for all interactions is hardly a basis for nihilism. We can cope perfectly well; we can benefit from

the experience of the first child, and we can use some procedures that we have used before. But because each child is a complex individual we must pay special attention to the differences among different children, and follow their lead. Our knowledge and experience coupled with our capacity to respond to individual situations is the way forward, and allows us to maintain our optimism.

The same is true with health care interventions. We must deepen our understanding of the nature of the interaction between health professionals and patients, and recognize its richness and its potential to deal with the complexities and uncertainties that always have and will continue to confront this interaction in the future. This book is a big step in this direction.

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Preface to the first edition

Around 600 BC, Daniel of Judah conducted what is probably the earliest recorded clinical trial. He compared the health effects of a vegetarian diet with those of a royal Babylonian diet over a ten day period.[1] Despite the dramatic findings of the study, over 4 centuries elapsed before publication of the results. The trial had obvious deficiencies by contemporary methodologic standards (allocation bias, ascertainment bias, confounding by Divine intervention),[2] but the publication has remained influential for over two millennia.

Other controlled clinical studies with methodologic weaknesses but important effects on practice have been undertaken during the ensuing centuries. Ambrose Paré (1514–1564), in an unplanned experiment, found that applying a soothing 'digestive medicament' to battle wounds produced better results than the traditional practice of cauterizing wounds with boiling oil.[3] Inoculation to prevent smallpox became popular after Maitland conducted a trial upon six Newgate convicts in 1721,[3] although the numbers treated and the precision of the trial were not adequate to give a fair picture of the effects of the procedure. Jenner published his famous studies on vaccination at the end of the eighteenth century, based on 10 and 14 persons. Appalled by the ravages of scurvy among ships crews on long voyages, in 1747 James Lind conducted a comparative trial of the most promising scurvy cures, using as subjects 12 sick seamen on board the Salisbury at sea. 'The most sudden and visible good effects were perceived from the use of the oranges and lemons.' The British Navy did not supply lemon juice to its ships until 1795.[3]

The nineteenth century saw many major advances. Probably the most sophisticated trial of a preventive type was a before/after study conducted by Ignaz Semmelweis in 1847. He noted that maternal mortality was much higher among women delivered by physicians and medical students, who were in frequent contact with cadavers at autopsies, than among women delivered by pupil midwives. After considering various hypotheses he reasoned that 'the cadaveric particles clinging to the hands are not entirely removed by the ordinary method of washing the hands', and introduced

the practice of more thorough washing and disinfectant.[4] Maternal mortality among the doctor-delivered mothers dropped by 50 per cent in the subsequent six months, although still not to as low a level as that achieved by the midwives.

Credit for the modern randomized trial is usually given to Sir Austin Bradford Hill. The historic MRC trials on streptomycin for pulmonary tuberculosis[5] are rightly regarded as a landmark that ushered in a new era of medicine. Their influence on the science of therapeutic evaluation was strengthened because the charismatic Hill followed up that work up with lectures and articles[6] reinforcing his message. Since Hill's pioneer achievement randomized trial methodology has been increasingly accepted, and the number of randomized controlled trials reported has grown exponentially. The current issue of the Cochrane Library[7] lists 158,065 such trials, and they have become the underlying basis for what is currently called 'evidence-based medicine'. The concept has rightly been hailed as a paradigm shift in our approach to clinical decision making.[8]

It is not, however, the first such paradigm shift. A similar scientific revolution was hailed more than a century and a half ago, by the editor of the American Journal of Medical Sciences in 1836, in his introduction to an article which he considered to be 'one of the most important medical works of the present century, marking the start of a new era in science'. It was 'the first formal exposition of the results of the *only true method of investigation* (emphasis added) in regard to the therapeutic value of remedial agents'. The article that evoked such effusive praise was the French study on bloodletting in the treatment of pneumonia by PCA Louis.[9,10]

At that time blood-letting was the almost universally accepted 'proper' method of treating pneumonia. Louis used the quintessential Baconian approach, of gathering vast amounts of data, which allowed him to make comparisons and systematically investigate the efficacy of treatments. His conclusion from that study was a bombshell; that the apparent efficacy of bleeding for pneumonia is a mere therapeutic illusion. His contribution to clinical epidemiology was to base recommendations for therapy on the results of collective experience, rather than on limited individual experience, tradition, or theory.

Louis's approach, and his evangelical zeal in promoting his methods created considerable controversy. He attracted many foreign disciples, including Oliver Wendell Holmes and William Osler

who made their mentor's work available to American readers. He also attracted strong opposition, and his work was mired in controversy. His opponents were numerous and vociferous. 'The physician called to treat a sick man is not an actuary advising a company to accept or deny risks, but someone who must deal with a specific individual at a vulnerable moment'. 'Averages could not help and might even confuse the practising physician as he struggles to apply general rules to a specific case.' Practising physicians were unwilling to hold their decisions in abeyance till their therapies received numerical approbation, nor were they prepared to discard therapies validated by both tradition and their own experience on account of somebody else's numbers.[10]

Although doubtless they arose partly from an innate resistance to change, and partly from misguided self-interest, the arguments against a widespread application of the so-called numerical approach stemmed largely from a lack of understanding of its intent. When both practitioners and public finally became aware that collective experience enhanced, rather than replaced, the clinical skills of the individual physician, Louis' numerical approach became the basis of medical research and literature until the midpoint of this century. It was by no means a panacea, but was an enormous step on the way towards more effective health care.

The arguments heard against the numerical approach in the last century are remarkably similar to those used against evidence-based medicine today. Worries are still being expressed that evidence-based medicine confuses statistics with reality, results in a loss of clinical freedom, and ignores the importance of clinical experience and of individual values.[11] These concerns stem from the mistaken belief that the proponents of evidence-based medicine claim a multicentre double blind placebo controlled randomized trial to be the only way to answer a therapeutic question. This, despite the fact that Austin Bradford Hill himself said 'Any belief that the controlled trial is the only way would mean not that the pendulum had swung too far, but that it had come right off its hook'.[12] Evidence-based medicine is simply the conscientious and judicious use of the current best evidence from clinical care research to guide health care decisions. It is another enormous step towards more effective health care. No more, and no less.

One reason for the sometimes expressed opposition to evidence-based medicine is a lack of understanding of the meaning of a randomized trial. This failure of understanding is not due to a paucity

of information; there is a vast literature about randomized trials, their purpose, their methodology, their limitations. Unfortunately, much of that literature has been incomplete, has been biassed, or has been couched in impenetrable jargon. It is not surprising that it has often been misinterpreted.

That is why this book is so welcome. It is written in clear, explicit, and understandable language, for those who use, would like to use, or should use, the results of randomized trials. It provides an accurate and comprehensive description of the randomized trial, its importance, when (and when not to) do a trial, how to interpret the results, when (and when not to) translate the results into health care decisions. It is a book to read, reflect on, learn from, use, and enjoy.

Murray W. Enkin
Dundas, 17 March 1998

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