Randomized Controlled Trials

Questions, Answers, and Musings

Second edition

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Questions, Answers, and Musings

Second edition

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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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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We thank the literary sources, including Lucretius and Austin Bradford Hill to whom we dedicated this book, and Archie Cochrane, Ivan Illich, Bruno Latour, and Mark Twain, who (among so many others) forced us to rethink many of our most cherished assumptions.

Finally, although most must remain unnamed, we thank our personal mentors, living and dead, never to be forgotten, who inspired us and taught us so much. The few that we name include George Browman, Beatriz Bechara de Borge, Iain Chalmers, Tom Chalmers, Mary Gospodarowicz, Marc Keirse, Mario Ruiz, Arturo Morillo, David Naylor, Bill Silverman, and Dave Sackett. They may not approve of all that we say in this book, but we are sure they will applaud our attempts to transcend the boundaries of conventional wisdom. They taught us that it is always healthy to challenge authority, especially our own.

Acknowledgments from the first edition

I would like to express my gratitude to all those, now anonymous, who asked me most of the questions that provided the structure of this book.

I would also like to thank a group of special people who have contributed significantly to my education as a clinician, researcher and teacher over the past 10 years. During my training in Colombia, Mario Ruiz exerted great influence on my research life, introduced me to the joy of clinical research and taught me the indelible meaning of the word mentor. German Parra showed me, for the first time, how research evidence can be integrated into clinical decisions, and Pedro Bejarano encouraged me, selflessly, to develop my research career abroad.

In England, Henry McQuay showed me the power of RCTs in health care and provided me with unprecedented conditions to nurture my curiosity and to speed up the development of my research skills. Iain Chalmers introduced me to systematic reviews and exemplified the meaning of collaboration. Chris Glynn showed me that busy clinicians can be researchers, provide humane patient care and have a rich personal life beyond medicine. His continuous challenges encouraged me to see the limitations of research evidence to guide health care decisions and motivated many of my efforts to overcome them. Clive Hahn encouraged me to write this book and Mary Banks, Senior Commissioning Editor (Books) at the BMJ Publishing Group made sure that it happened.

This book would have been much different without the influence of many of my colleagues at McMaster University. Some of them deserve special mention. I owe a lot to George Browman, who created the opportunity for me to come to Canada, expanded my research horizons, helped me to recognize the value of the research process and other types of information, and gave me unconditional support to develop my own agenda. I would also like to thank Brian Haynes, for re-reinforcing my notion of mentorship, and for helping me understand the need to integrate research evidence with the values, preferences and circumstances of the decision-makers. Geoff Norman introduced me to the principles of

cognitive and social psychology, opened my eyes to the limitations of human inference, encouraged me to focus the book on users of research, and challenged me continuously to recognize the barriers to the practice of evidence-based decision-making created by our human nature.

For advice on matters academic or personal, I have turned repeatedly to Murray and Eleanor Enkin, my favorite couple. My family and I feel immensely privileged to call them friends. We owe them a great deal for the warmth with which they have welcomed us into their lives, for their wisdom, and for their kind but always-candid advice. Murray read each of the chapters of this book, and gave me invaluable advice on both content and structure. Each contact with Murray and Eleanor, regardless of whether it centres on academic, family or cultural issues, is always a rich learning experience.

I would also like to express my gratitude to those who gave their time to me generously to help put this book together. Tracey Hillier, Geoff Norman and Iain Chalmers provided very constructive comments on the initial outline of the book. Susan Marks read, patiently, each of the chapters of the book, always giving me friendly and highly professional suggestions to improve their readability and structure. Judi Padunsky proofread most of the chapters, supported my communication with the publishers and organized the references for the whole book. Laurie Kendry and Mary Gauld read several chapters of the book and provided valuable input. Comments by Brian Haynes and Geoff Norman contributed enormously to the last chapter.

I owe more to my family than to anyone else. My extended family in South America showed me, from a very early age, the meaning of teamwork, unconditional support and trust. I could have not possibly written this book without Martha, my wife and best friend. Once more, her love, support and constructive criticism have helped me maintain a busy academic life and be part of a happy family. Finally, I would like to give special thanks to my daughters Alia and Tamen, for giving a new meaning to all I do.

Alejandro (Alex) R. Jadad

Introduction to the second edition

Why a second edition?

The value of randomized trials was already established in 1998 when Alex Jadad, as a newly established clinical researcher, wrote the first edition of this book. He wrote it to fill a need he had himself felt, for a 'comprehensive source of basic information about the underlying principles, methodology, and role of trials in health care decisions'. The methodology of RCTs had matured, there was a burgeoning acceptance of their value, but they were still not as widely understood or utilized as they should have been. He felt somewhat as the pioneer Bradford Hill must have felt in 1951, when he carefully explained the new concepts of the clinical trial, 'the highly organized and efficiently controlled therapeutic trial of new remedies'. If these had been properly used, he said 'we should have gained a fairly precise knowledge of the place of individual methods of therapy in disease, and our efficiency as doctors would have been enormously enhanced.'[1]

It did not take Bradford Hill long to recognize that clinical research was far more complex than he had originally thought. Less than 20 years after the first randomized trial[2] he noted that 'the present quality and scale of clinical trials are an increasingly serious bottle neck in the development and effective use of drugs', and 'there is a blind acceptance of double-blind trials without a critical evaluation of their short-comings and their ability to mislead as well as to lead'.

The need for a 'comprehensive source of basic information about the underlying principles, methodology, and role of trials in health care decisions' has remained unchanged as a new generation of researchers and clinicians have entered the health care field. What has changed since the first edition of this book is not randomized trials *per se*, but our recognition of the complexity of the world in which they are conceived, funded, carried out, disseminated, understood, used, and abused.

It is these wider questions that prompted our decision to provide a new edition of *Randomized Controlled Trials*. Randomized trials have not only influenced health care, they have also influenced

and been influenced by the local and global health care environment of which they are an integral part. We felt that it was time for a new look.

Why a new co-author?

Not really new. We have been close colleagues even before the first edition was started. Murray reviewed each chapter of *Randomised Controlled Trials* while it was under construction, and wrote the foreword to that edition. Although there is a 40-year difference in age between us, and we come from vastly different backgrounds, during more than a decade we have recognized the extent to which our paths and thinking have converged. We first noticed this in Oxford with our mutual interest in systematic reviews, and confirmed it at McMaster University as we became painfully aware of the pitfalls of over reliance on quantitative evidence and its limited influence on health care. During the past 5 years, our focus has been more on the value of rhetoric, information and communication technologies, complex systems, and the importance of effective communication in the health system.

Over the years, we have grown together in our understanding, have worked together on a variety of projects, and mutually reinforced our views on clinical evidence. We are happy to share our expanding vision of randomized trials in this new edition.

What is new in the second edition?

Those who offer or use health care still need a convenient and understandable source for basic information about randomized trials. Some chapters in the first edition provided this clearly, and in these, except for some newer and more current references, we have made only minor changes. Other chapters, however, have required more significant modifications, to incorporate the broader insights that have been gained during this period, as randomized trials have grown exponentially both in their number and their influence.

We have maintained the question and answer format that was so positively received by readers of the first edition, and kept the text free of formulas and unnecessary jargon. We have added a chapter on the ethics of randomized trials, which are not as simple and straightforward as we used to think that they were; we felt

that ethical considerations are every bit as important as methodology, and it is just as important to make them explicit.

Each chapter in the new edition ends with a section we call 'Our Musings'. In this section we go beyond the evidence or citations, and sometimes even beyond orthodox correctness to share our thoughts and concerns on the chapter topic with our readers. It has been exhausting, strenuous, and fun. We have learned more about randomized trials, about each topic, and about ourselves than we had believed possible. We hope that each reader will do their own musings on these topics, and, like the alchemists of old, transmute them into their personal elixir.

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Introduction to the first edition

This is a book for busy readers who need, wish or have to understand the basic principles of randomized controlled trials (RCTs) and their role in health care decisions. It is my best effort to fill a gap in the literature that was not able to fill with any single source during the past 15 years.

In the 1980s, as a medical student, intern, resident, and novice researcher, I could not find a single source that could help me really understand what RCTs were about, their strengths and limitations, and how to use them while making health care decisions. During that decade, I had to rely on many sources, most of which were written in a language that was difficult for me to understand, that presented information in formats that I could not adapt to my busy life or to my rapidly changing needs. I attributed my failed attempts to find a single, easy-to-read source of basic information to the fact that I was in Colombia, a developing country where it was often difficult to access the biomedical literature.

In 1990 I moved to England, where I spent 5 years as a research fellow, as a practicing clinician and as a graduate student. At the beginning of this period, the need for a good source of information to fill my most basic knowledge gaps intensified. My colleagues at Oxford were seasoned trialists. They not only designed and analyzed their own trials, but also criticized, quite strongly, trials done by others. As I did not want to bother my colleagues with basic questions (or to sound dumb), I started looking, again, for a source of information that could meet my most immediate needs. To my surprise, I could not find one. I started to list my questions and decided to get answers as soon as possible, from as many sources as necessary. I spent vast amounts of time (and not insignificant amounts of money) trying to get small pieces of information from different books, most of which targeted doers of research, not users. I also started asking for key references from colleagues, and tracked down articles mentioned by speakers at conferences or included in the reference lists of the articles I was collecting from other sources. As my list of questions grew, so did my list of references and contacts. After a while, I felt more comfortable to talk to

my colleagues about trials, started to design and lead some trials myself, and was invited to coordinate journal club sessions, where the work of others was rigorously appraised. Two years after my arrival in Oxford, one of my RCTs was published in The Lancet! This experience, however, created another set of challenges. Colleagues started to invite me to give lectures on pain research and trial design. I found myself under a different type of pressure. I had the opportunity, for the first time, to transmit to others what I had learnt. I began to feel confident about acknowledging my own uncertainties and knowledge gaps. People seemed to like my presentations and I started to receive invitations to give lectures. It did not take me long to realize that the attendees were asking similar questions from lecture to lecture, and that those questions were similar to those I had listed before. I started recording the questions and made every effort to address them during each successive lecture. As a result, the original questions gave way to new questions. Soon, some of the new questions from the audience started to coincide with my own questions at the time. I kept adding the new questions to my list for the 5 years I was in England. The questions I collected, approximately 100, form the backbone of this book.

In 1992, I was accepted as a graduate student at the University of Oxford and started to work on a thesis on meta-analysis of randomized trials in pain relief. As part of my thesis work, I coded over 15,000 citations and created a database with over 8,000 RCTs. I also led the development of what is regarded by many as the first validated tool to appraise the quality of RCTs, and created new statistical methods to combine data from different RCTs addressing the same topic. When I tried to use the newly developed methods to answer clinical important questions, I realized that despite having thousands of RCTs at my fingertips, relevant data were often unavailable or poorly reported. I also started to formulate questions about RCTs that had not yet been answered at all and became interested in the design of methodological studies to answer them. During this period, I started to meet people who shared my interest in addressing unanswered methodological questions. Most of them had published a number of studies that looked at the RCT as the subject of research, rather than as the research tool. Through my interaction with this different breed of researchers and their work, and my own methodological studies, I became aware of how vulnerable the RCT can be to bias, imprecision, irrelevance and