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Behavioral Clinical Trials for Chronic Diseases

Scientific Foundations

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This book is dedicated to

Thomas A. Deutsch, MD,
former Dean of Rush Medical College.

In taking a leap of faith,
he inspired a pursuit of excellence.

Acknowledgments

The inspiration for this book came from the Fellows of the US National Institutes of Health Summer Institute on Behavioral Randomized Clinical Trials. Over its first 19 years, the Institute trained over 800 Fellows in behavioral clinical trial methodology. These Fellows contributed to the evolving methodology in behavioral trials with their questions. Although the diseases and treatments varied from Fellow to Fellow, and from year to year, their questions were much the same. They were less interested in *how* to do something than they were in *why* they should do it. These questions informed the choice of topics for each of the chapters as well as the style of presenting them. I want to acknowledge the leadership of Peter Kaufmann who conceived, founded, and led the Summer Institute from its beginning in 2000, and Kate Stoney who later assumed leadership and pulled it off with equal success. I also want to acknowledge the support provided by the US National Institutes of Health Office of Behavioral and Social Sciences Research, which was initiated by Peter Kaufmann and continued by Raynard Kington, David Abrams, Bob Kaplan, Bill Riley, and Christine Bachrach.

This book's focus on the integration of good science and good methods came from my inspirational sabbatical year at the Center for Advanced Study in the Behavioral Sciences at Stanford University. During that year, scientists from diverse areas of behavioral sciences, including philosophy, political science, law, psychology, sociology, evolutionary biology, anthropology, linguistics, economics, geography, history, public affairs, public health, and literature, presented their work. These diverse disciplines pursue behavioral problems from different perspectives, contribute a piece of a puzzle, and together progress knowledge. The Center encouraged us to look beyond the science of any single discipline in pursuit of excellence within our own. I would like to extend my sincerest admiration and gratitude to Margaret Levi, the charismatic Director of the Center, for her vision and for the many ways she encouraged discovery through cross-fertilization.

All chapters have been reviewed by at least two junior or senior investigators with interests and expertise in behavioral clinical trials. These reviews were not always easy, as is clear from such comments as – "*I have no idea what you are trying to say!" "You have completely missed the point.*" But they helped us to see weaknesses and enhance strength. A special shout-out goes to Rachel Wu who reviewed and commented on every single chapter. Her basic science studies led her to make a creative leap to interventions. To do so, she needed to "*learn about this stuff.*" All of these reviewers are listed in the Appendix. We thank them sincerely for their help.

On a more personal level, I would like to thank Bob Kaplan for his ongoing encouragement. He has written 21 books; this was my first. He never stopped asking for progress reports, providing tips, and normalizing the challenges. He expected success, and it was infectious. I would also like to thank Rick Reiss for his emotional support. After long hours at the computer on a beautiful summer day, he would describe what his day had been like on the outside, helping me to experience vicariously a post-book life. I am hoping that my family and friends, particularly Celeste Fraser, will now give me a second chance after several years of declining their many invitations.

And finally to Joyce Mack, my faithful Assistant, I give my heartfelt thanks. Joyce worked on every reference, figure, table, and formatting problem, obtained all the permissions, and served as a liaison between me and many moving parts of this book. She did this with a commitment to excellence, and a sense of ownership, that was equal to mine.

Lynda H. Powell
(On behalf of my coauthors, Ken Freedland and Peter Kaufmann)
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Contents

About the Authors

Lynda H. Powell, PhD is the Charles J. and Margaret Roberts Professor of Preventive Medicine, Medicine, Behavioral Sciences, and Pharmacology and Chair of the Department of Preventive Medicine at Rush University Medical Center in Chicago. She received her doctoral degree from Stanford University in counseling psychology and began her academic career in chronic disease epidemiology at Yale University's School of Public Health. She has been a past principal investigator of five major randomized behavioral trials and has served as a standing member of the NHLBI Clinical Trials Study Section. She co-developed the ORBIT model for behavioral treatment development. She is a founding faculty member and former co-director of the NIH/OBSSR Summer Institute on Randomized Behavioral Clinical Trials. She is interested in sustained lifestyle change and its impact on reduction of cardiometabolic risk and is recognized internationally as an expert in the design, conduct, analyses, and interpretation of behavioral clinical trials. She is a Fellow of the Academy of Behavioral Medicine Research, the American Psychosomatic Society, and the Society of Behavioral Medicine.

Kenneth E. Freedland, PhD is Professor of Psychiatry and Psychology at Washington University School of Medicine in St. Louis and the Editor-in-Chief of *Health Psychology*, the official journal of the Society for Health Psychology. He received his doctoral degree in clinical psychology from the University of Hawaii and began his academic career at Northwestern University Medical Center in Chicago. He has been on the faculty at Washington University since 1986 where his research has focused on depression, self-care, and other psychosocial and behavioral problems in patients with heart disease. He has served as a standing member of the NHLBI Clinical Trials Study Section and is the Program Director of the NIH/OBSSR Summer Institute on Randomized Behavioral Clinical Trials. He has published multiple papers on behavioral trial methodology, particularly the selection and design of comparators, and feasibility and pilot studies. Dr. Freedland is a past president of the Academy of Behavioral Medicine Research and a Fellow of the Society of Behavioral Medicine, the American Psychological Association, and the American Heart Association.

Peter G. Kaufmann, PhD is Professor and Associate Dean of Research at the Villanova University College of Nursing. He received his doctorate in psychology from the University of Chicago and conducted post-doctoral research in neuroscience at Duke University. After joining the National Heart, Lung, and Blood Institute of the National Institutes of Health, he led research on mechanisms through which behavioral factors influence cardiovascular risk, and developed a program of research on evidence-based behavioral medicine. He is an expert in the conduct of multisite randomized behavioral trials for cardiovascular risk factors such as stress, depressive symptoms, and health behaviors. He founded the NIH/OBSSR Summer Institute on Randomized Behavioral Clinical Trials and is widely known for his expertise in clinical trial methodology. Dr. Kaufmann is a Fellow of the Academy of Behavioral Medicine Research and past president of the Society of Behavioral Medicine.

Chapter 1
Introduction

"You cannot solve a problem by continuing to use the same solutions that created the problem in the first place."
Albert Einstein

WINDOW OF OPPORTUNITY

The window of opportunity has never been opened wider for the integration of evidence-based behavioral treatments into clinical care. This opportunity has been created within the context of the current healthcare crisis and by the promise of behavioral treatments to cut, rather than to shift, costs.

The healthcare crisis is a problem of simple arithmetic. America and most other developed countries are graying in slow motion. Figure 1.1 presents a comparison of the distribution of ages in the American population in 1990, 2000, and as it is projected to be in 2025 [1].

The dark bars in Fig. 1.1 represent the baby boomer cohort, born between 1946 and 1964 and accounting for the largest segment of the population. In 1990 they entered the workforce, reaching their peak earning power in 2000. Their large numbers, compared to the relatively small number of retired elderly who have the greatest need for health care, made social programs such as Social Security and Medicare viable. Their large numbers also made it possible to develop a high-tech healthcare system that evolved into the most expensive, but not the most effective, in the world [2].

L. H. Powell et al., *Behavioral Clinical Trials for Chronic Diseases*,
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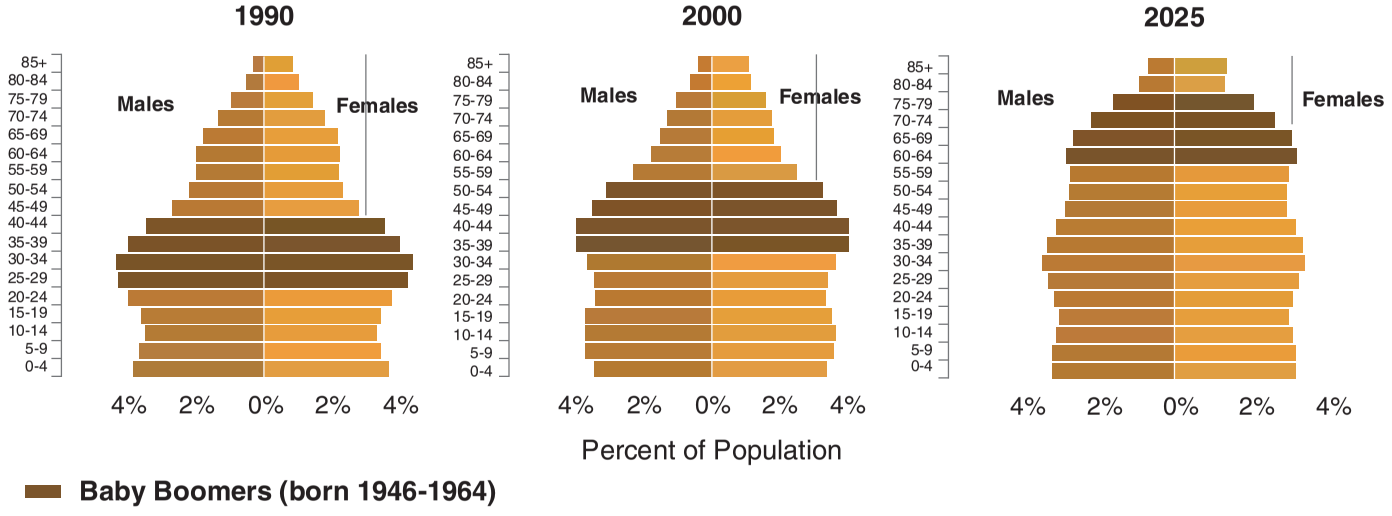


Fig. 1.1 US age distribution in 1990, 2000, and as projected in 2025

This picture changes as the baby boomers reach the ages of 60–79 and retire. By 2025, a large majority of them will be drawing on, rather than contributing to, Medicare and Social Security. But more elderly baby boomers will need health care than contributions from smaller, younger, and healthier cohorts can support. When Social Security was first rolled out in 1940, there were 45 workers for every Social Security-eligible retiree. When Medicare was signed into law in 1965, this ratio had dropped to approximately five workers to every retiree. In 2030, this ratio is projected to be only two workers to every retiree [3].

This is a problem of supply and demand. It is being felt by patients who see their deductibles and co-pays in their health care plans rising faster than their incomes. It will not be neutralized by pumping more money into health care. Despite having the most expensive healthcare system in the world, the United States ranks only 31st among nations in life expectancy [2]. Various approaches to healthcare reform offer proposals for shifting costs, resulting in battles between red and blue states, federal and state governments, private and public coverage, and pro-regulation liberals and free-trade conservatives.

Within this context, the window of opportunity opens for preventive behavioral interventions if they can cut, rather than shift, costs. Regardless of the time in a person's life when a behavioral intervention is introduced—the prenatal period, infancy, childhood, adolescence, adulthood, or older adulthood—the fundamental goal is to extend health and compress morbidity into the short period immediately preceding a death at old age.

Interest in prevention is increasing. The Affordable Care Act mandates that private insurers provide evidence-based preventive services without shifting costs to patients. Third-party payers and employers offer financial incentives for healthy behaviors. Medical providers receive financial incentives for achieving control of cardio-metabolic risk factors that have fundamental roots in lifestyle. Quality improvement initiatives target the "triple threat" of improving patient experience, improving the health of populations, and reducing per capita costs [4], all of which require effective behavioral strategies.

THE EVIDENCE: OBSERVATIONAL STUDIES

People are living longer but not necessarily in good health. Morbidity and chronic disability now account for one-half of the healthcare burden in the United States [5]. The link between these problems and health behaviors is irrefutable. Large-scale American and international epidemiologic studies, with sample sizes ranging from 20,000 to 1.6 million, have consistently shown that engaging in at least three health

behaviors, including such things as eating five servings of fruits and vegetables on most days, not smoking, and being physically active for 30 minutes on most days, is associated with 12–14 years of additional life expectancy, a 75% reduction in all-cause mortality, a 65% reduction in cancer mortality, an 82% reduction in cardiovascular mortality, and a reduction in risk for Alzheimer's disease and dementia [2, 6–10].

Many believe that genes are the primary determinant of one's health. But studies of cardiovascular disease and dementia have challenged this assumption. When lifestyle and genetic predisposition are examined simultaneously, a healthy lifestyle provided protection for all people regardless of whether they are at low, medium, or high genetic risk [11, 12]. This means that people can overcome their inherent genetic risk for major chronic diseases by engaging in lifestyle behaviors that are neither extreme nor exceptional.

Despite the enormous value of healthy living, the percentage of the American population living a healthy lifestyle is low and decreasing. In 1996, only 8.5% of Americans reported engaging in at least four healthy behaviors. In 2007, this rate dropped to 7.7% [9]. A suboptimal lifestyle translates into an increase in cardiometabolic risk. The prevalence of the metabolic syndrome, defined as having three out of five cardio-metabolic risk factors, all of which have fundamental roots in lifestyle, has increased over the past ten years from one-quarter to one-third of the American population [13].

Too many people lead unhealthy lifestyles. They are over-treated with tests, procedures, and medicines with high price tags and underwhelming results. The single greatest opportunity to improve health, reduce premature death, close the gap between health span and life span, and reduce healthcare costs lies in personal behavior.

THE EVIDENCE: INTERVENTION STUDIES

Many would argue that there is substantial and sound evidence to support the efficacy of behavioral interventions. But compared to the irrefutable link between behavior and chronic diseases in observational studies, evidence for the value of behavioral interventions to *reduce* chronic diseases is suboptimal. Admittedly, there is a large *quantity* of behavioral intervention studies. But they are often small refinement studies with a focus is on dimensions of a behavioral treatment, or they are small *Phase II* trials with a focus on improving behavioral or biomedical risk factors. Both of these types of studies have limited clinical importance.

There is a vacuum of evidence from definitive behavioral trials with clinically important outcomes such as costly acute events, deaths, hospitalizations, remission, and

recurrence. A powerful example of this vacuum comes from a review of all of the *Phase III* trials that have been conducted on either exercise or drug interventions for the secondary prevention of cardiovascular events. This review showed that 96% of the patients across all of these trials were enrolled in the drug trials, not the exercise trials, despite the equal efficacy of these two treatments in preventing mortality [14].

When a *Phase III* behavioral trial does find benefit, it is influential. The Diabetes Prevention Program showed that patients who were insulin-resistant and given a lifestyle intervention had a 58% lower incidence of diabetes than placebo and a 31% lower incidence than metformin [15]. These findings led to a new generation of effectiveness trials, third-party reimbursement for the lifestyle program, and implementation in community and clinical settings.

We do not need a greater *quantity* of evidence. We need a greater *quality* of evidence. The *Phase III* Diabetes Prevention Program trial provided the type of data that influenced clinical practice guidelines which, in turn, influenced third-party reimbursement, implementation into clinical practice, and a reduction in healthcare costs.

WHY WE WROTE THIS BOOK

We wrote this book because we are hoping to advance a culture of methodologically sophisticated PhD and MD investigators who have the vision, commitment, and depth of perspective to develop behavioral treatments and progressively test them using the standards that have come to be the norm in the medical sciences.

> *"An expert is a man who has made all of the mistakes which can be made, in a narrow field."*
>
> Niels Bohr
> Nobel Prize in Physics, 1922

We wrote this book because we are experts in behavioral clinical trial methodology using the definition articulated by Niels Bohr, the Danish physicist and philosopher who won the 1922 Nobel Prize in Physics for his work on quantum theory (see box). We forgive Dr. Bohr for excluding women from this quote. Mistakes are certainly divided evenly across genders. But the point is that we have devoted, and continue to devote, our careers to behavioral trials and therefore have the dubious distinction of having made mistakes across all of their aspects—design, operations, oversight, and interpretation. These experiences have led to our humility in the face of the many challenges behavioral trials impose. We echo the more eloquent and moving words of Jadad and Enkin [16].

> ***"Probably for too many years, we have designed, conducted, published, systematically reviewed, synthesized, taught, critiqued, lived with, and suffered with randomized controlled clinical trials. We have experienced the tremendous satisfaction … the valuable contribution they have made to health care and human health … and their potential and promise. … But above all, we experienced humility."***

We wrote this book to provide some insight into the common questions with which investigators pursuing careers in behavioral trials struggle. We have mentored over 800 Fellows who have participated in the NIH-OBSSR Summer Institute for Behavioral Trials over the past 19 years. These Fellows conduct behavioral clinical trials for interventions ranging all the way from individual behavior to policy, and outcomes across the entire range of organ systems. Although the classes change from year to year, the questions they tend to ask are the same. These questions have informed the content of each of the chapters in this book.

Understanding principles, mistakes, consequences, and ways to avoid them can foster deeper insight into how to make the many difficult design decisions that are needed in behavioral trials. We do not want new investigators to follow in our footsteps. We want them to seek what we sought, but in ways that are better informed, more sophisticated, and more successful.

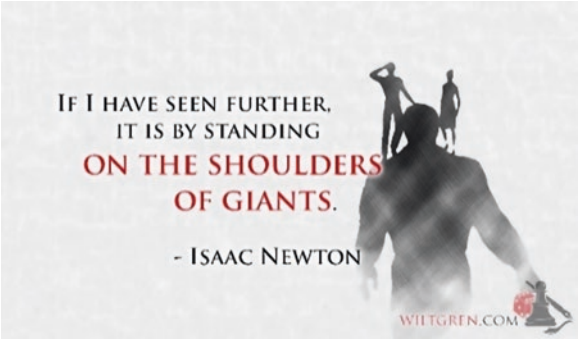
ORGANIZING PRINCIPLES

The chapters in this book focus on basic principles of behavioral clinical trial design. The choice of topics was based upon their fundamental importance, the challenges they present when a trial is behavioral in nature, and the dilemmas they can create for investigators. Each chapter features three organizing principles.

"Why Should You?" Rather Than *"How To"*

The clinical trial, and behavioral clinical trial, literature features papers and books that focus on "*how to*" use specific procedures to solve specific problems. The focused nature of this literature necessarily limits its ability to justify "*why should you?*" within the larger context of the competing decisions that characterize the design, conduct, and analysis of behavioral clinical trials.

We have tried to get at the "*why should you?*" by appealing to what constitutes good science. We begin each chapter with scientific principles derived from the scientific method. We present descriptions of the scientific process as articulated by the great philosophers



of science, scientists, and statisticians whose innovations form the basis of how we practice science today. We describe the history of our struggles to answer the question of whether or not a treatment works, and the evolution of the clinical trial as the best solution. If we can, in Newton's words, "*stand on the shoulders of giants,*" we can see further.

Each chapter then continues with a presentation of one or more basic principles, how they can create a problem for behavioral clinical trials, an approach to solving the problems, and the consequences that have occurred when a principle was compromised. The idea is to foster a commitment to preserving the basic principle and an openness to considering new ways to do so. We hope that discussions of "*why should you?*" will, in turn, encourage a search for the right approach to "*how to*," drawing on the extensive literature that now exists in papers and books on clinical trials and behavioral clinical trials.

Progressive Translational Science Model

This book focuses on behavioral clinical trials that seek to improve chronic disease outcomes. A progressive translational science model going all the way from discovery through to a confirmatory *Phase III* efficacy trial and beyond is well-suited to this purpose. Although translational science models extend to effectiveness, dissemination, and implementation studies, we do not focus on them here because we believe that the biggest roadblock to dissemination and implementation is the paucity of successful *Phase III* efficacy trials. Those with interests in these studies should consult the extensive literature that has developed in these areas.

A Comparison of Selected Design Elements in Behavioral Clinical Trials: The Status Quo and a Translational Model

STATUS QUO	TRANSLATIONAL MODEL
Single comprehensive trial	Progression of studies and trials
Refinement studies and *Phase II* trials	Push to *Phase III* trials
Exploratory studies	Confirmatory trials
Effectiveness without efficacy	Efficacy precedes effectiveness
Statistical significance	Clinical significance
Miniature efficacy trials	Feasibility and plausibility
Fear of failure	Welcome failure
Representative participants	Targeted participants
"Hard sell" recruitment	Pros and cons of participation
Innovation	Replication
Moderators, mediators, mechanisms	Minimization of multiplicity in outcomes
Rugged individualism	Networks

The progressive translational model encourages a long-term commitment to a behavioral intervention where failure is expected, refinement is encouraged, and results from one study inform the design of the next. This model is consistent with the cultural movement that is evolving in the applied behavioral sciences, which has been energized by the need to enhance the uptake of behavioral treatments into clinical practice, and advanced by the emergence of a "metascience" of behavioral clinical trial methods [17]. *(See Chapter 12: Epilogue.)*

We do not simply present the status quo and what may be viewed currently as "best practices" in behavioral trial design. Instead, we seek to identify specific areas in a progressive translational science model where an alternative to the status quo exists. The box compares the status quo with a translational model on a sampling of specific design elements that will be found in more detail throughout this book.

Cross-Disciplinary Methods

When a behavioral treatment seeks to improve a chronic disease endpoint, its progressive evaluation is a cross-disciplinary undertaking. The most appropriate design and methods vary depending upon where in the treatment development process a study is placed. For example, refinement studies are often about exploring various treatment options such as the optimum mode, dose, and agent of change. The exploratory experimental design methods, embedded within the behavioral sciences, are well-suited to accomplishing such aims. Alternatively, confirmation of the value of a behavioral treatment on a chronic disease outcome often requires long follow-up periods for disease outcomes to accumulate. The methods of double-blind drug trials, developed within medicine and epidemiology, handle such data optimally. Beyond this, a behavioral clinical trial often faces challenges that cannot be solved within any particular discipline. The inability to double-blind a trial, and the difficulties in choosing an optimal comparator, pose unique problems for behavioral trial design that often need solutions that synthesize wisdom across many disciplines.

Each chapter features cross-disciplinary methods as they are brought to bear on specific challenges in behavioral clinical trial design. Since the application of these methods varies depending upon where in the treatment development process a study is placed, efforts have been made to distinguish among exploratory studies, refinement studies, *Phase II* trials that seek to confirm the value of a behavioral treatment on a behavioral or biomedical outcome, and *Phase III* trials that seek to confirm the value of a behavioral treatment on a chronic disease outcome. Once the phase of treatment development is defined, the optimal phase-specific methods are considerably easier to identify.

THE AUDIENCE

Anyone with an interest in the design, conduct, analysis, or interpretation of randomized behavioral clinical trials aimed at improving chronic disease endpoints would benefit from reading this book. Use of the term "behavioral"is for purposes of simplicity. This book applies to the design of trials for any non-drug treatment, including those at the behavioral, social, environmental, or policy level, where intervention development is needed, double-blinding is not possible, and progression to definitive clinical outcomes is anticipated.

We are especially interested in reaching junior scientists at the beginning of their research careers. Behavioral scientists are sophisticated in the treatment side of the behavioral clinical trial. They have expertise in developing behavioral treatments and can therefore design the kind of treatments that could actually improve definitive clinical outcomes. For this group, the topics found in this book can encourage a push beyond a sole focus on refinement and early testing, toward confirmatory trials with clinically important health outcomes.

Medical scientists are sophisticated in the chronic disease side of the behavioral clinical trial. A growing number have interests that go beyond finding the right medicine, device, or surgical procedure for their patients. They seek to find solutions to behavioral problems such as improving adherence to therapies, ability to communicate, quality of care, and proactivity in their patients. The topics found in this book can foster an appreciation of the developmental work that is needed to prepare a behavioral treatment for testing in a confirmatory behavioral trial.

Policy-makers, funders, and third-party payers who have interests in behavioral approaches for improving chronic diseases may find this book valuable. It could help them to identify ways to assess rigor in behavioral trials and thus assess the quality of the evidence they need to make good decisions.

And for those who do not work in any field of science, this book can be helpful in determining how much trust to place in a new behavioral trial evaluating a novel behavioral treatment, such as a new diet. Trust can be increased by knowing the specific aspects of a trial that determine its rigor. Rather than reading the technical descriptions within each chapter, an understanding of what to look for can be enhanced by the simple overview presented as the "*Fundamental Points*" which begin each chapter.

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Chapter 2
Quality of a Clinical Trial

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
Goethe (1749–1832)

Fundamental Point

There is a mismatch between the standards for "evidence-based" treatments set by medicine and the evidence that exists for the value of behavioral treatments. In medicine, the highest-quality evidence comes from Phase III efficacy trials, with important clinical outcomes, and clinical trial methods. Evidence for behavioral treatments more often comes from Phase II efficacy trials, with outcomes that are behavioral or biomedical risk factors, and experimental methods. A progressive, translational model for behavioral treatment development and evaluation can encourage a push toward more high-quality Phase III behavioral trials that meet the standards expected by medical gatekeepers and third-party payers and enhance the potential for implementation of behavioral treatments into clinical practice.

To close the gap between evidence-based behavioral treatments for chronic diseases and their uptake in clinical practice, this book aims to encourage the development of evidence for the value of behavioral treatments that meets the standards for quality existing in medicine. Evidence for quality is strongest in *Phase III* efficacy trials which follow the agreed-upon "rules" for clinical trial methods. In the behavioral clinical trial literature, there are many more *Phase II* than *Phase III* trials. What is needed is not a larger quantity of such evidence, but a higher quality of evidence using the standards that exist in medicine. This book applies a progressive, translational science model to achieve that goal.

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SCIENTIFIC PRINCIPLES

The overall aim of this book is to close the gap between evidence-based behavioral treatments for chronic diseases and their uptake in clinical practice. At least one reason for this gap is a discrepancy between what is meant by "evidence-based." What is evidence in one beholder's eye may not be evidence in another's. It could mean evidence from any randomized trial. It could mean evidence from a specific type of randomized trial. It could mean evidence from any well-designed and well-conducted systematic inquiry, including observational data, clinical reports, or pilot studies.

A basic premise of this book is that since the gatekeepers for chronic disease management are medical practitioners, the onus is on the behavioral trialist to conduct a trial using the same standards they use to evaluate any medical treatment. Positive trials that meet these standards for quality can become integrated into clinical practice guidelines [1, 2]. This is the pathway to reimbursement for a treatment by third-party payers [3] and implementation into clinical practice.

This premise makes it useful to examine the standards for high-quality evidence and high-quality clinical trials that have been set in medicine.

High-Quality Evidence

To understand what "high-quality" evidence means in medicine, consider the criteria used by national and international committees charged with grading the quality of evidence for medical treatments, as reported by the Institute of Medicine [4]. Table 2.1 summarizes the criteria used to achieve the highest-quality rating. The criteria are remarkably similar. Regardless of the specific committee doing the rating, they are consistent in judging the highest quality of evidence to be that coming from high-quality randomized controlled trials (RCT's). Although the existence of one well-designed clinical trial provides strong evidence, replication of results from several trials carried out by different investigators enhances the strength of the evidence and moves the rating from "strong" to "very strong."

High-Quality Trials

Since the above review committees consistently refer to "high-quality" randomized trials, it is of interest to consider what is meant by this. That is, what are the fundamentals that make a clinical trial one of high quality?

Table 2.1 Requirements for the highest quality of evidence for a treatment across a variety of international rating systems [4]

COUNTRY	SYSTEM	HIGHEST-QUALITY RATING	REQUIREMENTS
International	Grading of Recommendations, Assessment, Development, and Evaluation Working Group (2009)	High	RCT
United Kingdom	Centre for Evidence-Based Medicine (2009)	1a	Reviews of high-quality RCTs are consistent
		1b	Single RCT with narrow confidence interval
Scotland	Scottish Intercollegiate Guidelines Network (2009)	1+ +	Reviews of RCTs with very low risk of bias
		1+	RCT with low risk of bias
New Zealand	New Zealand Guidelines Group (2007)	A	≥ 1 review or RCT rated as 1^{++} and directly applicable to target population
Canada	The Canadian Hypertension Education Program (2007)	A	RCT with blinded assessment, intent-to-treat analysis, follow-up and sample size sufficient to detect clinically important difference
United States	Institute for Clinical Systems Improvement: 157 Medical Groups in Minnesota (2003)	A	RCT which is free of doubts about bias, design flaws, generalizability
	Strength of Recommendation Taxonomy, American Family Physicians (2004)	Level 1	Consistent good-quality patient-oriented RCTs or a high-quality individual RCT
	US Preventive Services Task Force (2008)	High	Consistent results from well-designed and conducted studies in representative primary care populations
	American College of Cardiology/American Heart Association (2009)	A	Data derived from multiple RCTs
		B	Data derived from single RCT
	American Academy of Pediatrics (2004)	A	Well-designed RCTs on relevant populations
	American Academy of Neurology (2004)	Class I	Prospective RCT with masked outcome, representative population, clear primary outcome, defined inclusions/exclusions, low rate of dropouts and crossovers, baseline characteristics equivalent across arms
	American College of Chest Physicians (2009)	High	RCTs without important limitations
	National Comprehensive Cancer Network (2008)	High	High-powered RCTs or meta-analyses
	Infectious Disease Society of America (2001)	I	Evidence from >1 properly randomized trial

Most of what we know about the fundamentals of clinical trials comes from the design of double-blind drug trials. This topic has been the focus of an extensive literature, much of which has been summarized in a large number of papers and a wide range of books [5–28]. These fundamentals developed rapidly since the 1950s when clinical trials became more popular, missteps became more common, and the need to prevent these missteps rose. These fundamentals are now referred to as the "rules" of clinical trials and have wide acceptance in the medical community. One of the classic texts for these basic principles is the *Fundamentals of Clinical Trials* [20] now in its 5th edition. Table 2.2 presents a selection of some of the fundamental principles of clinical trials presented in this classic text. They pertain primarily to *Phase III* double-blind drug trials and focus on maximizing internal validity and minimizing alternative explanations for results. These rules are articulated by reviewers of clinical trial papers submitted to high-quality journals. If they are not followed, the paper is often rejected, and it generally ends up in journals with less visibility and lower impact.

Table 2.2 Selected fundamental "rules" of clinical trials [20]

TREATMENT DEVELOPMENT	Well-defined progression: *Phase I* (dose), *Phase II* (biologic activity), *Phase III* (efficacy), *Phase IV* (effectiveness)
PURPOSE	Single primary question with secondary questions carefully justified and surrogate measures evaluated primarily in early-phase studies
POPULATION	Well-defined with high likelihood of detecting hypothesized results by having high risk for the primary outcome, high likelihood of adhering to the treatment protocol, and no competing adverse events
DESIGN	Randomized allocation to treatment or control to minimize confounding and invalid statistical tests
SAMPLE SIZE	An approximation, derived from conservative assumptions
ADHERENCE TO TREATMENT	Select participants who will adhere to treatment. Maximize adherence by careful participant selection, simple treatment protocols, intensive monitoring, and a variety of remediation strategies
RETENTION IN TRIAL	Estimated rate of withdrawal from the trial is pre-specified and minimized by careful participant selection, simple trial protocols, intensive monitoring, a variety of retention strategies, and, if needed, reduction of final assessment battery to the primary endpoint only
PRIMARY OUTCOME	One clinically relevant primary endpoint, often an event rate with a long follow-up
MONITORING	Independent monitoring of data quality, safety, and adherence, with a limited number of pre-planned tests to detect early harm, benefit, or futility
ANALYSES	Intent-to-treat with no exclusions for any reason to avoid bias of unknown magnitude and direction resulting from compromised random assignment. Minimal missing data which is generally not at random
REPORTING	Obligation to report not only results but also whether trial worked as planned