

Clinical Research Methods for Surgeons

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*To our mentors, colleagues, and trainees,
whose collective experiences have been essential
to the conceptualization and compilation of this text*

Foreword

With his keen analytical mind and penchant for organization, Charles Darwin would have made an excellent clinical investigator. Unfortunately for surgery, his early exposure at Edinburgh to the brutality of operations in 1825 convinced him to reject his father's plan for his career and pursue his interest in nature. His subsequent observations of how environmental pressures shaped the development of new species provided the essential mechanism to explain evolution and the disappearance of those species that failed to adapt. Today, surgeons face the same reality as new technology, progressive regulation by government and payers, medico-legal risks, and public demands for proof of performance force changes in behavior that our predecessors never imagined.

We know that surgeons have always prided themselves on accurate documentation of their results, including their complications and deaths, but observational studies involving a single surgeon or institution have given way to demands for controlled interventional trials despite the inherent difficulty of studying surgical patients by randomized, blinded techniques. That is why this book is so timely and important. In a logical and comprehensive approach, the authors have assembled a group of experienced clinical scientists who can demonstrate the rich variety of techniques in epidemiology and statistics for reviewing existing publications, structuring a clinical study, and analyzing the resulting data. As these techniques become incorporated as standards into the curriculum of medical, public health, and nursing schools, the surgical professions must include them in their graduate training programs, professional meetings, and reporting practices. To ignore these new standards is to risk failing to continue to attract the best and brightest students into the field and becoming labeled as more technologically than scientifically advanced.

Recent evidence suggests that even the most rigorously designed randomized clinical trial can be corrupted by biased reporting or data withheld on adverse events. The potential threat of industry control of such information must be a part of the training and review process as clinical research becomes more dependent on industry funding. Full disclosure of business relationships between industry and clinician-investigators has been a good start in defining ethical limitations, but it is essential that full disclosure include the registry of all clinical trials in a national database as recommended by the Consolidated Standards of Reporting Trials statement (*Ann. Intern. Med.* 2004; 141:781–788) and adopted by the International Committee of Medical Journal Editors in 2004. These editors declared that its members would not publish the results of trials that had not been publicly registered, and most surgical journals have followed this lead. Currently there are several registries in existence and the World Health Organization is working on an online portal that would bind these databases into a single source.

Darwin taught us that change in response to environmental pressures is essential to survival of the species, and leads not only to successful adaptation, but also to new

directions for potential development. Surgeons have always been leaders in exploring new fields and this book will be a useful guide to better methods of clinical research. We should be grateful to the authors for pointing the way; the rest is up to us.

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Preface

Clinical research is the branch of scientific endeavor devoted to the evaluation of patients and the analysis of associated health outcomes. These analyses serve to identify potential areas for change in physician or patient behavior or in clinical processes. Implicit in the concept of clinical research is the notion that the findings will be used to modify clinical practice to achieve better outcomes. As such, clinical research has always been a necessary prerequisite for the advancement of surgery as a practice.

In the past decade, basic science research in the surgical disciplines has advanced at a dizzying pace. Clinical research in surgery, however, has lagged far behind surgical basic science research. For example, the selected case series from a single academic center still remains one of the most common study designs employed by surgeons who address clinical research questions, despite the known limitations of this design. Although such clinical research techniques were appropriate 50 years ago—when the primary focus was on advances in surgical technique—they are inadequate for addressing the broader policy issues and clinical management questions faced by the surgeon today. The clinical research questions facing surgeons in the 21st century require sophisticated research techniques that most surgeons are, at best, only vaguely familiar with and, at worst, completely unfamiliar with.

Evidence-based medicine is the foundation on which clinical research is built and is the explicit use of scientific data in decision making for clinical care. It is as critical to surgical practice as to any other medical discipline. A requisite for evidence-based practice is the availability of high levels of evidence. Our colleagues in internal medicine have successfully adopted clinical research methods and have disseminated this information to trainees and practicing physicians through textbooks, educational series, and fellowship programs, such as the Robert Wood Johnson Clinical Scholars Program. Although it may be tempting to use existing resources to educate surgeons in clinical research methods, one must remember that diseases requiring surgical treatment are often unique, and that many of the methods used for looking at research questions in internal medicine are not easily applied to the surgical fields. Patients faced with the prospect of a major surgical procedure must often deal with physical and psychological challenges as a result of treatment that are quite distinct from those facing patients undergoing medical therapy for chronic illness. Existing methodologies used in internal medicine, pediatrics, or other nonsurgical fields will fail to capture some of the distinct aspects in surgical diseases. It is incumbent on the surgeon-scientist to understand clinical research methodology and to develop new techniques for addressing important research questions. This need for new well-trained clinical researchers, and original clinical research in the surgical fields, is so great that funding agencies such as the National Institutes of Health, the American College of Surgeons, the American Academy of Head and Neck Surgeons, and the American Urological Association Foundation have specifically allocated research funding to assist in the development of physicians with formal training in clinical epidemiology and health services research to improve clinical research

in the surgical disciplines. This trend will no doubt increase in the coming years as the complexity of clinical research questions further increases.

The purpose of *Clinical Research Methods for Surgeons* is to provide the surgeon with an easy-to-use guide for interpreting published clinical research. With so many articles published even in the most arcane of surgical journals, the need to separate the wheat from the chaff requires one to be critical when reviewing the study design and methods for each article. This book is also intended to serve as a reference guide for the surgeon who wishes to conduct clinical research either to answer scientific, hypothesis-driven questions or simply to evaluate his or her outcomes. The book itself is divided into four parts. The first provides a general overview of the infrastructure of clinical research. It describes the thought process required for undertaking new studies and discusses both the ethical and financial issues involved in running a clinical research unit. It should be of particular interest to young surgeons who are about to undertake new studies. The second part describes specific study designs and statistical techniques used in clinical research, whereas the third part describes methods for assessing clinical outcomes. These two sections will be of interest to both investigators interested in performing clinical research and those who are just reviewing the literature and applying it to their practice. Finally, the last section addresses special research techniques and topics that will certainly be of interest to the active investigator. As a whole, *Clinical Research Methods for Surgeons* provides insights to the clinical investigator and clinician reading the literature.

It is our sincere hope that the text will allow the reader to have a clear understanding of clinical research methods. However, it is still highly recommended that the surgeon develop collaborations with an experienced analyst or a biostatistician if the surgeon himself or herself has no such expertise. This is no different than in basic science research, where the mantra has been to train surgeons as “translational scientists” to bridge the gap between the laboratory and the bedside. So the same applies to clinical research where we need to bridge the gap between epidemiological/statistical science and the bedside.

Although it is always tempting for a surgeon to report his or her “experience” on a topic, it is important to recognize that this does not provide high levels of evidence and will undoubtedly not change practice. High-quality surgical research takes time, involves planning, and, most importantly, requires an appreciation of methods and the clinical setting. If a clinical research project is worth doing, then it is worth doing right. Surgeons must be open minded about learning new clinical research methods so that horizons can be expanded and patient care improved. Failure to do so may lead surgery to become stifled and allow other parties to dictate the care of surgical patients. In the end, use of high-quality clinical research methods is a necessity for the surgical discipline as our practices expand with new basic science discoveries and new surgical techniques, and as other scientific discoveries abound. The reader is encouraged to become familiar with these methods and to incorporate them into his or her surgical practice. In this new millennium, the enlightened clinical researcher/surgeon must command a thorough understanding of the latest methodologies for analyzing clinical data. It is our sincere hope that this text will be the first step in that direction.

David F. Penson, MD, MPH
John T. Wei, MD, MS

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