

Preface

A preface is an opportunity for you and me to share an amiable conversation before the serious work starts. If you give me a moment, I will share with you my motivations for writing an introductory text about the statistical monitoring of clinical trials, a staple of modern research efforts in healthcare.

I am pleased to have been involved in clinical research for eighteen years. Many of my efforts focused on preparations for and presentations to Data Monitoring Committees (DMCs), each of which was tasked with overseeing the conduct of a particular clinical study. During these activities, I have spoken with many clinicians about the epidemiology and biostatistical foundation of this mode of clinical research.

In my experience, nothing confuses a DMC member as do these so-called “stopping rules” for monitoring the conduct of a healthcare research study. The idea of prematurely ending a study makes intuitive sense to the clinical members of the committee. The rules themselves with their arcane terminology are the problem. Descriptions of “group sequential procedures” and “stochastic curtailment” provide no useful handholds for the clinician working to understand this slippery but essential subject. The fact that neither medical school nor residency curricula discuss any of the details of these procedures is one possible explanation for the continued lack of understanding among clinicians. In general, the non-statistical members of newly conceived DMCs in the 21st century are just as confused about statistical monitoring guidelines as were their clinical predecessors who sat on DMCs in the 1980s.

A major reason for this continued confusion is that clinical investigators, although blessed with the motivation to do research, commonly do not have strong mathematical backgrounds. Although many have worked hard to develop the basic understanding of epidemiology and biostatistics necessary to be an effective investigator, the underlying mathematical details of commonly used monitoring procedures as frequently presented remain beyond the scope of their training.

Of course, the statistical literature has much to say on the subject of monitoring rules in clinical research. Beginning with the manuscripts of Armitage and Wald in the 1940s, the statistical treatment of this topic slowly expanded until the late 1970s, when it exploded. The recognition of the importance of the monitoring of clinical research, in concert with the complexity of the underlying mathematics has attracted the best and the brightest of biostatisticians. Their devotion to the study of the underlying mathematical structure of monitoring procedures has resulted in a body of knowledge that is both evolutionary and illuminating. However, because it tends to be scripted in the technical and exclusionary language of advanced mathematics, the writing tends to enlighten only the sophisticated analyst.

The text by Christopher Jennison and Bruce Turnbull [1] is a fine example of a comprehensive treatment of a difficult statistical subject.

The technical writing style that has been implemented in the field of “interim monitoring” should come as no surprise. However, work in this area, propelled forward by the strong rowing of capable statistical theorists, can leave the clinical investigator behind in its wake. Required to apply complex processes that they do not understand, the clinical investigator commonly finds little introductory material available. In addition, clinical researchers with no quantitative background have difficulty communicating with biostatisticians or experienced trial methodologists who have much experience but little time to explain these issues to their inexperienced colleagues. Thus, investigators who wish to learn about these mathematical procedures are hard pressed to identify readily understandable source material.

The purpose of this text is to fill that gap. If you know nothing about monitoring guidelines in clinical trials, then this book is for you.

I have chosen to begin this book with a brief history of monitoring rules in clinical research. Although this is the first chapter in this book, it needn't be the first chapter that you read. Being nontechnical, it might be most useful to view its contents as a pleasant oasis in a desert of more complicated discussion. Its considerations of the interactions between scientists serves to convey something about the people who were involved in these important historical efforts. The observation that the epidemiologist Bradford Hill suffered from tuberculosis years before he helped design an early clinical trial to study this disease may be a mere curiosity to some; to others it helps to explain his intellectual fortitude in working with skeptical clinicians.

For the same reason, I have broken up some of the technical arguments that appear in later chapters with an occasional vignette. As my students frequently remind me, it is best to have a joke close by when discussing anything mathematical.

I must confess that this is not a book about the operation of DMCs. That material has been very nicely developed in *Data Monitoring Committees in Clinical Trials: A Practical Perspective* by Susan Ellenberg, Thomas Fleming, and David DeMets (John Wiley & Sons, Ltd., West Sussex, 2002). Their text is very broad in scope, focusing on the DMCs evolution and contemporary operation. Our focus here is on statistical monitoring procedures that these DMCs devise and utilize, not on the DMCs themselves.

One final note. An important segment of the current clinical investigator population is comprised of women. Therefore, I have alternated the use of gender in the hypothetical illustrations offered by this text. Although this is the most illustrative and the least exclusionary approach, it does require mental alacrity on your part as the genders change from example to example.

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References

1. Jennison C, Turnbull BW. (2000). *Group Sequential Methods with Applications to Clinical Trials*. New York. Chapman & Hall/CRC.



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Fundamentals for Investigators

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