

(68) John Whitehead (1983)

The Design and Analysis of Sequential Clinical Trials

Chichester: Ellis Horwood

Preamble

This was only the second text on sequential clinical trials to be published during the thirty-six years period from 1948 to 1983. Its predecessor *Sequential Medical Trials* by Peter Armitage first appeared in 1960 (see no. (6) above) with a second edition in 1975 (see no. (32) above). Like its predecessor, Whitehead's book also went to a second edition published in 1992, and beyond to a revision in 1997. Originally it appeared in the Ellis Horwood *Series in Mathematics and its Applications* (Series Editor: Professor GM Bell (Chelsea College, University of London)) devoted mainly to technical texts in pure and applied mathematics; the revised second edition moved to the Wiley *Statistics in Practice* Series (Editor: Vic Barnett).

Aims

Most clinical trials recruit patients over a period of several months or years, and the results of the trial accumulate steadily throughout its duration. For ethical reasons the trial should involve the smallest number of patients necessary for it to reach a conclusion. The trial designs which form the subject of this book have been created with these features of clinical trials in mind. My objective has been not only to describe such designs but also, by providing extensive tables, to facilitate the choice of a suitable design and the eventual analysis of a sequential trial. Although some of the methods described here have been known for many years, few clinical trials have yet made use of them. The principal readership of this work will inevitably be medical statisticians, although an attempt has been made to separate the most theoretical passages from the rest of the text in order to encourage study by interested clinicians. It is also hoped that the book will prove useful for students of clinical trials and of sequential analysis (Preface, page 11).

Contents (272 pages)

[Sub-sub headings omitted]

Preface (John Whitehead)

1. Clinical trials

- 1.1 The rationale of clinical trials
- 1.2 Historically and prospectively controlled studies
- 1.3 Within and between subjects comparisons
- 1.4 General design features
- 1.5 Sample size criteria
- 1.6 Sequential designs
- 1.7 An example of a sequential clinical trial and the plan of this book
- 1.8 Bibliographic notes and further comments

2. Allocating patients to treatments

- 2.1 The purpose of allocation schemes
- 2.2 Stratification variables
- 2.3 Allocation schemes using a single categorisation
- 2.4 Allocation schemes using several categorizations
- 2.5 Allocation to more than two treatments
- 2.6 Bibliographic notes and further comments

3. Measurement of treatment difference

- 3.1 Measures of difference and information
- 3.2 Quantitative within subjects comparisons

- 3.3 Binary within subjects comparisons
- 3.4 Quantitative between subjects comparisons
- 3.5 Ordinal between subjects comparisons
- 3.6 Binary between subjects comparisons
- 3.7 Comparative survival studies
- 3.8 The general form of the test statistics
- 3.9 Bibliographic notes and further comments
- 4. The design of a sequential trial
 - 4.1 Introduction
 - 4.2 Monitoring a clinical trial
 - 4.3 The triangular test
 - 4.4 The double triangular test
 - 4.5 The sequential probability ratio test
 - 4.6 Interim analysis
 - 4.7 Sequential clinical trials with non-constant or unpredictable inspection intervals
 - 4.8 The theory of the sequential probability ratio test
 - 4.9 The theory of the triangular test
 - 4.10 Bibliographic notes and further comments
- 5. The analysis of a sequential trial
 - 5.1 Decision making and inference
 - 5.2 The calculation of significance levels
 - 5.3 Estimation of treatment difference
 - 5.4 Estimation of treatment effects
 - 5.5 Overrunning
 - 5.6 Very early stopping
 - 5.7 The truncation of sequential procedures
 - 5.8 Theoretical details
 - 5.9 Relationship with likelihood methods
 - 5.10 Bibliographic notes and further comments
- 6. Partially sequential procedures
 - 6.1 Fully and partially sequential procedures
 - 6.2 Restricted procedures
 - 6.3 Repeated significance tests
- 7. Prognostic factors
 - 7.1 Introduction
 - 7.2 The theory of the generalised linear model
 - 7.3 The sequential analysis of generalised linear models
 - 7.4 Special cases of the generalised linear model
 - 7.5 Simulated clinical trials
 - 7.6 Bibliographic notes and further comments
- 8. The comparison of more than two treatments
 - 8.1 Introduction
 - 8.2 Elimination procedures
 - 8.3 Orthogonal comparisons
 - 8.4 Bibliographic notes and further comments

Appendix A: Tables for use in the design and the analysis of sequential clinical trials

Appendix B: Simulated data used in the examples of section 7.5

References

Index

Author

The author is John Whitehead BA, MSc, PhD (Department of Applied Statistics, University of Reading, England).