

(6) Peter Armitage (1960)
Sequential Medical Trials
Oxford: Blackwell

Preamble

This is the first single-author comprehensive textbook on clinical trials written by a medical statistician. It is also the first textbook to include sample size Tables (distributed throughout the book) **and confidence intervals**. That it is devoted to sequential clinical trials as opposed to fixed sample-size, parallel-group trials may be a surprise. However, the sequential approach to experimentation was developed in the context of weapons research undertaken during the Second World War when there was a need to produce proficient munitions. The adaptation of these methods to medicine was at least a beneficent outcome.

There is a facsimile of the frontispiece at the James Lind Library (www.jameslindlibrary.org/waife-so-shapiro-ap-1959). For the second edition published in 1975 see no. (32) below.

Aims

It is now widely accepted that the most reliable way to compare the effectiveness of alternative medical treatments is to carry out a controlled trial, in which the treatments are allocated at random. In recent years a number of these trials have been conducted by sequential methods, and there appears to be a growing interest in this development. In a sequential analysis the observations are examined as they become available, and the total number of subjects to enter the trial, is not predetermined, but depends on the accumulating results. Sequential analysis has an immediate appeal in clinical research. Patients normally enter an investigation serially and a continuous scrutiny of the results is usually quite feasible. Rather more important is the ethical consideration, which requires that any unnecessary use of inferior treatments should be avoided. The investigator will, therefore, frequently wish to bring a trial to an early close if an important difference can, at that early stage, be established. The present time seems a suitable moment to attempt a general survey of this topic. There are now a sufficient number of examples of medical trials conducted by sequential analysis to show that the methods are practicable. Unfortunately, the basic information about these methods has been scattered through the statistical and medical literature, and the few expository papers are neither comprehensive nor up-to-date. I have attempted in this book to write an account of the principles underlying the subject, and to provide sufficient detail about the methods to enable the medical practitioner to proceed without necessarily feeling obliged to consult a statistician. Most of the techniques are simple, and are conveniently carried out by plotting points on charts. I have omitted as much mathematics from the text as possible (Preface).

Contents (105 pages)

Preface

- 1 Medical trials
 - 1.1 Introduction
 - 1.2 Comparative experimentation
 - 1.3 The problem of medical experimentation
 - 1.4 Experimental design

- 1.5 Statistical analysis: tests, decisions and estimates
- 1.6 The amount of experimentation
- 1.7 The tendency to experiment sequentially
- 2 Sequential experimentation
 - 2.1 The nature of sequential experimentation
 - 2.2 Reasons for sequential investigations
 - 2.3 The choice of a stopping-rule
 - 2.4 Circumstances making sequential methods unsuitable
 - 2.5 Pairing and randomisation
 - 2.6 The comparison of more than two treatments
- 3 Evaluation by preferences
 - 3.1 General
 - 3.2 Types of preference
 - 3.3 Open designs
 - 3.4 Closed designs
 - 3.5 Exact significance level
 - 3.6 Confidence limits for θ
 - 3.7 Skew designs
 - 3.8 The choice of a design
- 4 Comparison of two proportions
 - 4.1 Introduction
 - 4.2 The derived series of preferences
 - 4.3 The choice of a design
 - 4.4 Confidence limits for $\pi_1 - \pi_2$
 - 4.5 Some examples
 - 4.6 The use of matched pairs
- 5 Measurements with known variability
 - 5.1 Introduction
 - 5.2 Open designs
 - 5.3 Closed designs
- 6 Measurements with unknown variability
 - 6.1 Introduction
 - 6.2 Open designs
 - 6.3 Closed designs
 - 6.4 Skew designs
 - 6.5 The number of observations required
- 7 Follow-up studies
 - 7.1 General considerations
 - 7.2 The comparison of response times
- 8 Other types of investigation
 - 8.1 Introduction
 - 8.2 Comparisons against a fixed standard
 - 8.3 Estimation procedures
- 9 Misconceptions and difficulties
 - 9.1 Some misconceptions: economy and significance; preliminary assumptions

9.2 Some difficulties: change of boundaries; combination of results; the multivariate problem; interactions; the effect of various factors

Appendix: Notes on statistical theory

A.1. General

A.2. Two-sided open designs

A.3. Two-sided closed designs

A.4. Computations for binomial designs

References

Author index

Subject index

Author

The author is Peter Armitage MA, PhD (Statistical Research Unit of the Medical Research Council, London School of Hygiene and Tropical Medicine).