

Dictionary *for* Clinical Trials

Second Edition

Simon Day

*Roche Products Limited,
Welwyn Garden City, UK*



John Wiley & Sons, Ltd

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To Nikki, Anya and Huw

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Preface to the Second Edition

I had a simple hope (but perhaps a difficult one to achieve) that this *Dictionary for Clinical Trials* would be a helpful and pragmatic little reference book to a wide variety of people working in clinical trials. The first edition proved a great success. I am grateful to the various reviewers who made kind comments; I also respect one or two more critical reviewers who pointed out some shortfalls (indeed, one or two blatant errors); and I thank the many colleagues and friends who have given me positive feedback. Without doubt, one of the greatest compliments was from Professor Sakuma, who felt it worth the effort to translate the first edition into Japanese.

Overall that simple hope has been achieved but the science and business of clinical trials is still relatively young and fast-moving. I have therefore tried to update a little, to include terms that were only just emerging at the time of the first edition and to delete a few that are, perhaps, redundant. Of course, to the best of my ability I have corrected the known errors. I have also introduced numerous commonly used abbreviations (and their meanings). These were an intentional omission from the first edition (with only one or two privileged exceptions) but they now enjoy an equal status in this second edition.

I hope this second edition continues to be helpful to a wide variety of ‘doers’ and ‘consumers’ of clinical trials.

Preface to the First Edition

It is now fifty years since the British Medical Research Council published the results of a trial entitled ‘Streptomycin treatment of pulmonary tuberculosis’ (*British Medical Journal*, 30 October 1948, pp. 769–782). That study is widely regarded as the first randomized clinical trial. Earlier examples of non-randomized studies are cited, notably that of J. Lind (*A Treatise on the Scurvy*, 1753). Despite such a history and the enormous numbers of trials conducted and published in the last twenty or so years, many people do not consider ‘clinical trials’ as a discipline in its own right and, as such, the breadth of terms that should be covered in a dictionary of this kind is not well defined. Ultimately, the choice of entries is a personal one, guided by experiences of what I have had to learn and what my colleagues in various specialties of the clinical trials spectrum have struggled to understand. Additionally I have trawled clinical trial protocols, reports, regulatory guidelines and published manuscripts to try to cover the majority of terms that are likely to be encountered. A lot of the terminology of clinical trials is statistical: terms used for the design (blocks, randomization, stratification) and for the analysis (confidence interval, *P*-value, survival analysis, *t* test, to list but a few). I make no apology for the high proportion of statistical terms: those are usually the ones that are least well understood. Overall though, the content is broad and it is very difficult to summarize what is covered.

It is almost as difficult to summarize what isn’t covered. This is not a dictionary of medical terms, of statistical terms, of epidemiological, ethical or data management terms. It does, however, contain elements of all those disciplines, the first three in particular. Many of the epidemiological terms included would not ordinarily be found in a clinical trial protocol or report; however, in the discussion of whether a clinical trial is appropriate for answering a particular medical question, or in discussion of trial results alongside other sources of evidence, the issue of other approaches such as case-control studies and cohort studies is likely to be discussed. I have not included specific diseases (a medical dictionary would be more appropriate) or names of clinical rating scales but I have included a variety of medical terms that are frequently assumed to be understood (terms such as acute, chronic, subcutaneous, etc.). Abbreviations

are not included, except in the few instances where a term is better known by its acronym than by its full name (COSTART and MedDRA are obvious examples). Nor are the names of professional or scientific societies, research institutions or regulatory authorities included.

The intended readership for this dictionary are all those people who work with clinical trial protocols and reports or who otherwise need to understand the use of language in this specialist area. Such a readership includes clinical trialists (those people who actually carry out the various administrative, clerical and scientific aspects), those who sit on ethics committees, those who work in regulatory departments or grant awarding bodies, doctors, nurses, pharmacists (and patients) reading clinical trial reports and so on. Trials sponsored by the pharmaceutical industry, as well as those conducted by academic institutions or by small groups of enthusiasts, all fall within the scope of this work, as do community-based intervention studies, vaccine trials, and studies of medical practice and medical devices. Necessarily, many entries will be more relevant to some types of trials and trialists than to others. I hope the coverage is adequate without being too cumbersome.

The style of explanations and definitions is aimed at being pragmatic and readable rather than purist. Pre-existing definitions (often in regulatory guidelines) have not necessarily been faithfully reproduced, although care has been taken to incorporate the essential meaning from relevant guidelines. As an example, the term 'adverse event' has a very specific definition within the International Conference on Harmonisation although the explanation given here is a little more brief. Further examples of pragmatism abound in the explanations of some statistical terms. Many statisticians may challenge the correctness of my explanations of analysis of covariance, Bayesian statistics or *P*-value, for example: I apologize to them in advance but hope that the explanations I have given will help those readers who understand little or nothing of such terms to at least gain a rough and ready grasp of their meaning. Similarly, 'ethics' is covered in a mere two lines: there are other related entries but the aim is to get the essential meaning across. Full and complete explanations of all the terms included would mean this work taking on the scale of a series of text books and that is not the intention. I hope that the explanations given here, put in the context where the word or expression has arisen, will allow most readers to unravel most uncertainties.

In my defence over accuracy and quality control I can claim that every single entry has been reviewed by a variety of my colleagues; and in their defence I acknowledge that every single error, discrepancy and inconsistency remains my responsibility.

The Ground Rules

The following is a brief guide to what's in and what's not in, and rules for cross-referencing related or alternative terms.

In general, *study* is used rather than *trial* except where the distinction is helpful (strictly speaking, study encompasses trial but many types of study will not be trials). Similarly, *trial* is taken to mean *clinical trial*. For example, *acute study* is listed, but not *acute trial* or *acute clinical trial*.

Phrases may sometimes be abbreviated but, I hope, without causing any difficulty in finding them. For example, *adaptive design* should be taken to encompass *adaptive trial design* and *adaptive clinical trial design*.

Where alternative terms may be used interchangeably I have tried to pick the most common term to define and its synonyms will simply direct you there with the symbol $\approx$. For example, *alpha error* simply says ' $\approx$ type I error' (where an explanation is given). The most important terms used within the definition of other terms are emboldened, as are references to contrasting terms ($\Leftrightarrow \dots$) and related terms ($\Rightarrow \dots$). I hope that sometimes giving an indication of contrasting or related terms may help understanding. It is inevitable, however, that some definitions will be circular: *active control* contrasts with ($\Leftrightarrow$) *placebo control*; *placebo control* contrasts with ($\Leftrightarrow$) *active control*. Ultimately, just as with all dictionaries, all definitions must use the terms herein to explain other terms and the circularity becomes inevitable.

Bibliography

There is a variety of books written about clinical trials, and several other dictionaries and glossaries that may prove helpful in defining terms and clarifying their use. The following titles have proved particularly helpful in compiling this dictionary and may serve as useful additional sources of reference.

Applied Clinical Trials (various issues)

Bégaud, B. (2000) *Dictionary of Pharmacoepidemiology*, John Wiley & Sons, Chichester.

Boyd, K.M., Higgs, R. and Pinching, A.J. (1997) *The New Dictionary of Medical Ethics*, British Medical Journal, London.

Bull, K. and Spiegelhalter, D.J. (1997) Survival analysis in observational studies. *Statistics in Medicine*, **16**, 1041–74.

Churchill's Illustrated Medical Dictionary (1989) Churchill Livingstone, New York.

Duncan, A.S., Dunstan, G.R. and Welbourn, R.B. (1981) *Dictionary of Medical Ethics*, revised edition, Darton, Longman and Todd, London.

Dupayrat, J. (1990) *Dictionary of Biomedical Acronyms and Abbreviations*, 2nd edn, John Wiley & Sons, Chichester.

Everitt, B.S. (2002) *The Cambridge Dictionary of Statistics in the Medical Sciences*, 2nd edn, Cambridge University Press, Cambridge.

Everitt, B.S. (2006) *Medical Statistics from A to Z*, 2nd edn, Cambridge University Press, Cambridge.

Fitzpatrick, S. (2006) *The Clinical Trial Protocol*, ICR Publishing, Marlow.

Fitzpatrick, S. (2006) *Clinical Trial Design*, ICR Publishing, Marlow.

Flather, M., Aston, H. and Stables, R. (eds) (2001) *Handbook of Clinical Trials*, Remedica Publishing, London.

Friedman, L.M., Furberg, C.D. and DeMets, D.L. (1998) *Fundamentals of Clinical Trials*, 3rd edn, Springer, New York.

Heister, R. (1989) *Dictionary of Abbreviations in Medical Sciences*, Springer-Verlag, Berlin.

- The Institute of Clinical Research (2006) *Medical Abbreviations Used in Clinical Trials*, ICR Publishing, Marlow.
- Jadad, A. (1998) *Randomised Controlled Trials*, British Medical Journal, London.
- Johnson, F.N. and Johnson, S. (1977) *Clinical Trials*, Blackwell Scientific Publications, Oxford.
- Last, J.M. (2000) *A Dictionary of Epidemiology*, 4th edn, Oxford University Press, New York.
- Machin, D., Day, S. and Green, S. (eds) (2006) *Textbook of Clinical Trials*, 2nd edn, John Wiley & Sons, Chichester.
- Marriott, F.H.C. (1990) *A Dictionary of Statistical Terms*, 5th edn, Longman Scientific and Technical, Harlow.
- Meinert, C.L. (1986) *Clinical Trials: Design, Conduct and Analysis*, Oxford University Press, New York.
- Meinert, C.L. (1996) *Clinical Trials Dictionary: Terminology and Usage Recommendations*, The Johns Hopkins University, Baltimore.
- Nahler, G. (1994) *Dictionary of Pharmaceutical Medicine*, Springer-Verlag, New York.
- Parry, T. (2006) *Statistics in Clinical Research*, ICR Publishing, Marlow.
- Pereira-Maxwell, F. (1998) *A–Z of Medical Statistics*, Arnold, London.
- Pocock, S.J. (1983) *Clinical Trials: A Practical Approach*, John Wiley & Sons, Chichester.
- Rasch, D., Tiku, M.L. and Sumpf, D. (1994) *Elsevier's Dictionary of Biometry*, Elsevier Science, Amsterdam.
- Raven, A. (1993) *Clinical Trials: An Introduction*, Radcliffe Medical Press, Oxford.
- Samson, P. (1975) *Glossary of Bacteriological Terms*, Butterworth and Co., London.
- Schwartz, D., Flamant, R. and Lellouch, J. (1980) *Clinical Trials*, Academic Press, London.
- Senn, S. (1997) *Statistical Issues in Drug Development*, John Wiley & Sons, Chichester.
- Spilker, B. (1991) *Guide to Clinical Trials*, Raven Press, New York.
- Spriet, A. and Simon, P. (1985) *Methodology of Clinical Drug Trials*, Karger, Basel.
- Steen, E.B. (1978) *Abbreviations in Medicine*, 4th edn, Baillière Tindall, London.

Bibliography

- Vogt, W.P. (1993) *Dictionary of Statistics and Methodology*, Sage Publications, London.
- Wang, D. and Bakhai, A. (2006) *Clinical Trials. A Practical Guide to Design, Analysis, and Reporting*, Remidica, London.
- Winslade, J. and Hutchinson, D.R. (1993) *Dictionary of Clinical Research*, Brookwood Medical Publications, Brookwood.



a posteriori after the event; generally referring to decisions made or actions taken after data or results of a study have been seen. ⇔ ***a priori***. ⇒ **Bayes' theorem, posterior distribution**

a priori before the event; generally referring to decisions made or beliefs held before data or results of a study have been seen. Such decisions or beliefs may be based on data from previous studies or subjective feeling based on informal clinical experience. ⇔ ***a posteriori***. ⇒ **prespecify, Bayes' theorem, prior distribution**

Abbé plot ≈ **L'Abbé plot**

abscissa ≈ **x axis**. ⇔ **ordinate** (or **y axis**)

absolute change the numerical difference between two numbers as in, for example, **change from baseline**. ⇔ **relative change**

absolute frequency the number of items or the number of occurrences of a specified event. Often abbreviated simply to frequency. ⇔ **relative frequency**

absolute risk the number of events (deaths, adverse reactions, etc.) divided by the number of individuals who could have experienced the event (or the number of people 'at risk' of the event). ⇔ **relative risk**

absolute value a numerical value that ignores any positive or negative sign; for example, the absolute value of +3 is +3; the absolute value of -3 is also +3

absorption the process by which drug enters the blood stream. ⇔ **clearance, elimination**

absorption study a study that measures the process of (particularly the time taken for) drug to be absorbed into the blood stream

accelerated failure time model a statistical model used in **survival analysis** that assumes the effect of one treatment is to multiply the median **survival time** for patients randomized to that treatment relative to that of patients randomized to another treatment. ⇔ **Cox's proportional hazards model**