Second Edition

Encyclopaedic Companion to Medical Statistics

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Foreword by Richard Horton, *The Lancet*

WILEY

Encyclopaedic Companion to Medical Statistics

Second Edition

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To Mary-Elizabeth
Brian S. Everitt

To Cathy-Joan, Laura, Carolyn and David
Christopher R. Palmer

Foreword

This encyclopaedia contains no entry for 'Peer review'. In my small corner of the medical statistical universe, this seems like a gross sin of omission. Instead, the process of evaluating research papers is discussed under 'Critical appraisal'. Are these two procedures synonymous? And, irrespective of whether they are or are not, should anybody care?

I believe that peer review and critical appraisal do differ, that these differences matter a great deal when considering the ways in which readers should interpret the medical literature, and that an understanding of these differences helps to place medical statistics in its proper context when surveying the wide horizon of clinical and public health research.

The editors of this quite wonderfully rewarding treatise on statistical terms have defined critical appraisal as 'the process of evaluating research reports and assessing their contribution to scientific knowledge'. This statement follows naturally from the meaning of the words 'criticism' (the art of judging) and 'appraisal' (the estimation of quality). That is to say, critical appraisal is an estimation of worth followed by some kind of judgment – a judgment that leans more towards an art than a science. As a non-statistician, I rather warm to the precise imprecision of this definition.

Now consider the more commonly embedded term 'peer review' and look how inferior it is! Who is this anonymous idealised peer? Generally, one would consider a peer to be an equal, somebody who comes from a group comparable to that from which the person under scrutiny has emerged. This intellectual egalitarian is subsequently set the task of viewing again (to take 'review' at its most literal meaning) the work under consideration. But to view with what purpose? None is specified.

Despite these practical shortcomings, editors of biomedical journals remain wedded to 'peer review'. We feel uncomfortable with the notion of critical appraisal. The embodiment of peer review as a distinct scientific discipline is the series of international congresses devoted to peer review in biomedical publication, organised jointly by *JAMA* and the *BMJ*. These congresses have spawned hundreds of abstracts, dozens of research papers, and four theme issues of *JAMA*. They are entirely commendable in every way. For the editors of *JAMA* and the *BMJ*, peer review encompasses a broad range of activities: mechanisms of editorial decision making, together with their quality, validity, and practicality, online peer review and publication, pre-publication posting of information, quality assurance of reviewers and editors, authorship and contributorship, conflicts of interest, scientific misconduct, peer review of grant proposals, economic aspects of peer review, and the future of scientific publication.

In other words, peer review is a tremendously elastic concept, allowing editors to stretch it to mean whatever interests them at a given (whimsical) moment in time and place. Indeed, its elasticity is seen by many of us as its great strength. The concept grows in richness and understanding as our own appreciation of its complexity and nuance soars. The impenetrable nature of peer review, and the obscure and hard-to-learn expertise it demands, feeds our brittle egos. The notion of critical appraisal, by contrast, is far thinner in meaning, with much less room for editorial manipulation and aggrandisement.

Even if peer review and critical appraisal do differ, should anyone actually care? Yes, they should, and for a very simple reason: the idea of peer review is now bankrupt. Its retention as an operation within the biomedical sciences reflects the interests of those who wish to preserve their own power and position. Peer review is fundamentally anti-democratic. It elevates the mediocre. It asphyxiates originality and it kills careers. How so?

Peer review is not about intelligent engagement with a piece of research. It is about defining the margins of what is acceptable and unacceptable to the reviewer. The mythical 'peer' is being asked to view again, after the editor, the work in question and to offer a comment about the geographical location of that work on the map of existing knowledge. If there is space on this map, and provided the work does not disrupt (too much) the terrain established by others, its location can be secured and marked by sanctioning publication. If the disruption is too great, the work's wish to seek a place of rest must be vetoed. Peer review is about the agency of power to preserve established orthodoxy. It has nothing to do with science. It has everything to do with ideology – and the maintenance of a quiet life of privilege and mystique.

Instead, critical appraisal is about incrementally working one's way towards truth[1]. It can never be about truth itself. The essence of biomedical research is estimation. Our world resists certainty. Critical appraisal is about transparent, measurable analysis that cuts a path towards greater precision.

1. Horton, R. 2002: Postpublication criticism and the shaping of clinical knowledge. *JAMA* 287, 2843–7.

Critical appraisal refuses to veil itself in the gaudy adornments that editors pin to peer review in order to embellish their own importance in the cartography of scientific inquiry. A far more robust instrument critical appraisal is for that refusal.

What do these differences tell us about the proper place of medical statistics in biomedicine today? In my view, as a lapsed doctor and a now wrinkled editor, medical statistics is the most important aspect of our critical appraisal of any piece of new research. The evaluations by so-called peers in the clinical specialties that concern a particular research paper provide valuable insight into how that work will be received by a community of practitioners or scholars. However, as an editor I am less interested in reception than I am in meaning[2].

I want a tough interrogation of new work before its publication, according to commonly agreed standards of questioning – standards that I can see and evaluate for myself. To return to my personal definition of critical appraisal, I want an estimation of quality combined with a judgment. I do not want a view from the club culture of one particular academic discipline. The rejection of peer review by the editors of this encyclopaedia is therefore a triumph of liberty against the forces of conformity.

Yet still today, too much of medicine takes medical statistics for granted. Time and again, we see research that has clearly not been within a hundred miles of a statistical brain. Physicians usually make poor scientists, and physicians and scientists together too often play the part of amateur statistician – with appalling consequences. The future of a successful biomedical research enterprise depends on the flourishing of the discipline we call medical statistics. It is not at all clear to me that those who so depend on medical statistics appreciate either that dependence or the fragility of its foundation.

If this magnificent encyclopaedia can be deployed in the ongoing argument about the future of twenty-first century academic medicine, then not only the research enterprise but also the public's health and well-being will be far stronger tomorrow than it is today.

Richard Horton
Editor, *Lancet*

2. Horton, R. 2000: Common sense and figures: the rhetoric of validity in medicine. *Satist Med* 19, 3149–64.

Preface to the Second Edition

In this second edition of the *Encyclopaedic Companion to Medical Statistics* there are over 30 completely new entries and the majority of entries from the first edition from 2005 have been revised and updated. The aim of this new edition remains the same as before and that is, quintessentially, to aid communication between medical researchers and statisticians.

We hope this aim has been met by providing fully cross-referenced articles encompassing a wide range of statistical topics likely to be encountered in today's medical literature, of suitable breadth and depth to give sufficient detail, but not to overwhelm with too much technical background and to provide helpful further references where needed for those wishing to explore topics more deeply. We believe a key strength of this single-volume reference work also remains from the first edition, namely the accessibility of the articles. Their readability is enhanced because contributors are not only experts in their respective fields but also adept at communicating statistical concepts to non-statisticians, including those who may admit to having a certain fear of handling data and not knowing how to deal with all the numbers arising from their medical research!

Another aspect of the aim to enhance communication between medical and statistical disciplines concerns encouraging timeliness of seeking statistical advice. It is our hope too that this *Encyclopaedic Companion* will serve to encourage medical researchers to consult with statisticians at the earliest opportunity within the life cycle of a research project. Relevant entries herein might be read before, and reviewed after, such consultations to enable clearer understanding and, ultimately, help facilitate better quality medical research.

Once again our thanks are due to a large number of people: the contributors for their sterling efforts in producing such excellent entries, the team at Wiley, in particular Richard Davies and Heather Kay and, of course, to our families.

Brian S. Everitt, Dulwich, London
Christopher R. Palmer, Cambridge, UK

Preface

Statistical science plays an important role in medical research. Indeed a major part of the key to the progress in medicine from the 17th century to the present day has been the collection and valid interpretation of evidence, particularly quantitative evidence, provided by the application of statistical methods to medical investigations. Current medical journals are full of statistical material, both relatively simple (for example, t-tests, p-values, linear regression) and, increasingly, more complex (for example, generalised estimating equations, cluster analysis, Bayesian methods). The latter material reflects the vibrant state of statistical research with many new methods having practical implications for medicine being developed in the last two decades or so. But why is statistics important in medicine? Some possible answers are:

(1) Medical practice and medical research generate large amounts of data. Such data are generally full of uncertainty and variation, and extracting the 'signal' from the 'noise' is usually not trivial.
(2) Medicine involves asking questions that have strong statistical overtones. How common is the disease? Who is especially likely to contract a particular condition? What are the chances that a patient diagnosed with breast cancer will survive more than five years?
(3) The evaluation of competing treatments or preventative measures relies heavily on statistical concepts in both the design and analysis phase.

Recognition of the importance of statistics in medicine has increased considerably in recent years. The last decade, in particular, has seen the emergence of evidence-based medicine, and with it the need for clinicians to keep one step ahead of their patients, many of whom nowadays have access to virtually unlimited information (much of it being virtual, yet some of it being limited in its reliability). Compared with previous generations of medical students, today's pre-clinical undergraduates are being taught more about statistical principles than their predecessors. Furthermore, today's clinical researchers are faced (happily, in our view) with growing numbers of biomedical journals utilising statistical referees as part of their peer review processes (see CRITICAL APPRAISAL and STATISTICAL REFEREEING). This enhances the quality of the papers journal editors select, although from the clinical researcher's perspective it has made publication in leading journals more challenging than ever before.

So statistics is (and are) prevalent in the medical world now and is set to remain so for the future. Clearly, clinicians and medical researchers need to know something about the subject, even if only to make their discussion with a friendly statistician more fruitful. The article on consulting a statistician quotes one of the forefathers of modern statistics, R.A. Fisher who, back in 1938, observed wryly: '*To consult the statistician after an experiment is finished is often merely to ask him to conduct a post-mortem examination. He can perhaps say what the experiment died of.*' Thus, one of our hopes for the usefulness and helpfulness of the *Encyclopaedic Companion to Medical Statistics* is that it may serve to encourage both productive and timely interactions between medical researchers and statisticians. Another sincere hope is that it fills a gap between, on the one hand, textbooks that delve into possibly too much theory and, on the other hand, shorter dictionaries that may not necessarily focus on the needs of medical researchers, or else have entries that are tantalisingly succinct. To meet these ends, the present reference work contains concise, informative, relatively non-technical, and hence, we trust, readable accounts of over 350 topics central to modern medical statistics.

Topics are covered either briefly or more extensively, in general, in accordance with the subject matter's perceived importance, although we acknowledge there will be disagreement, inevitably, about our choice of article lengths. Many entries benefit from containing real-life, clinical examples. Each has been written by an individual chosen not only for subject-matter expertise in the field but, just as importantly, also by ability to communicate statistical concepts to others.

The extensive cross-referencing supplied using SMALL CAPITALS to indicate terms that appear as separate entries should help the reader to find his or her way around and also serves to point out associated topics that might be of interest elsewhere within the *Encyclopaedic Companion*. All but the shortest entries contain references to further resources where the interested reader can learn in greater depth about the particular topic.

Thus, while hoping this work is found to be mostly comprehensible we do not claim it to be fully comprehensive. As co-editors we take joint responsibility for any errors ('sins of commission') and would positively welcome suggestions

for possible new topics to consider for future inclusion to rectify perceived missing entries ('sins of omission').

Our thanks are due to numerous people – first, to all of the many contributors for providing such excellent material, mostly on time (mostly!) with particular gratitude extended to those who contributed multiple articles or who handled requests for additional articles so gracefully. Next, we appreciated the tremendous and indispensable efforts of staff at Arnold, especially Liz Gooster and Liz Wilson, and not least for their remaining calm during an editor's moments of anxiety and neurosis about the entire project. In addition we would like to thank Harriet Meteyard for her constant support and encouragement throughout the preparation of this book. Finally, our family members deserve especial thanks for having been extra tolerant of our time spent on developing and executing this extensive project from beginning to end. It is our hope that the *Encyclopaedic Companion* proves all these efforts and sacrifices to be well worthwhile, becoming a useful, regularly-thumbed reference added to the bookshelf of many of those involved in contemplating, conducting or contributing to medical research.

Brian S. Everitt and Christopher R. Palmer
January 2005

Biographical Information on the Editors

Brian S. Everitt – Professor Emeritus, King's College London. After 35 years at the Institute of Psychiatry, University of London, Brian Everitt retired in May 2004. Author of approximately 100 journal articles and over 50 books on statistics, and also co-editor of *Statistical Methods in Medical Research*. Writing continues apace in retirement but now punctuated by tennis, walks in the country, guitar playing and visits to the gym, rather than by committees, committees and more committees.

Christopher R. Palmer, founding Director of Cambridge University's Centre for Applied Medical Statistics, regularly teaches and collaborates with current and future doctors. His first degree was from Oxford, while graduate and post-doctoral studies were in the USA (at UNC-Chapel Hill and Harvard). He has shifted from mathematical towards applied statistics, with particular interest in the ethics of clinical trials and the use of flexible designs whenever appropriate. Fundamentally, he likes to promote sound statistical thinking in all areas of medical research and hopes this volume might help towards that end. Chris served as Deputy or Acting Editor for *Statistics in Medicine*, 1996–2000, and is a long-standing statistical reviewer for *The Lancet*. He and his wife have three children they consider to be more than statistically significant.

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Abbreviations and Acronyms

ACES	Active control equivalence study
ACET	Active control equivalence test
AD	Adaptive design
AI	Artificial intelligence
AIC	Akaike's information criterion
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AR	Autoregressive
ARMA	Autoregressive moving average
AUC	Area under curve
BIC	Bayesian information criterion
BUGS	Bayesian inference Using Gibbs Sampling (software)
CACE	Complier average causal effect
CART	Classification and regression tree
CAT	Computer-adaptive testing
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CONSORT	Consolidation of standards of reporting trials
COREC	Central Office for Research Ethics Committees
CPMP	Committee for Proprietary Medicinal Products
CPO	Conditional predictive ordinate
CrI	Credible interval
CRM	Continual reassessment method
CSM	Committee on Safety of Medicines
CUE	Cost-utility analysis
CV	Coefficient of variation
CWT	Continuous wavelet transform
DAG	Directed acyclic graph
DALY	Disability adjusted life-year
DAR	Dropout at random
DCAR	Dropout completely at random
DDD	Data-dependent design
DE	Design effect
DoF	Degrees of freedom
DIC	Deviance information criterion
DM	Data mining
DMC	Data monitoring committee
DSMC	Data and safety monitoring committee
DWT	Discrete wavelet transform
DZ	Dizygotic
EBM	Evidence-based medicine
EDA	Exploratory data analysis
EM	Expectation-maximisation
EMEA	European Medicines Evaluation Agency
FDA	Food and Drug Administration
GAM	Generalised additive model
GEE	Generalised estimating equations
GFR	General fertility rate
GIS	Geographical information system
GLIM	Generalised linear interactive modelling (software)
GLIMM	Generalised linear mixed model
GLM	Generalised linear model
GLMM	Generalised linear mixed model
GRR	Gross reproduction rate
GWAS	Genome-wide association studies
HALE	Health-adjusted life expectancy
HMM	Hidden Markov model
HPDI	Highest posterior density interval
HREC	Human research ethics committee
HRQoL	Health-related quality of life
IBD	Identity-by-descent
ICC	Intraclass (or intracluster) correlation coefficient
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonization
IRB	Institutional review board
ITT	Intention-to-treat
IV	Instrumental variable
KDD	Knowledge discovery in databases
KM	Kaplan–Meier
kNN	k-nearest neighbour
LDF	Linear discriminant function
LR	Likelihood ratio
LREC	Local research ethics committee
LS	Least squares
LST	Large simple trial
MA	Moving average
MANOVA	Multivariate analysis of variance
MAR	Missing at random
MCA	Medicines Control Agency
MCAR	Missing completely at random

MCMC	Markov chain Monte Carlo
MHRA	Medicines and Healthcare Products Regulatory Agency
MLE	Maximum likelihood estimate (or estimation)
MREC	Multicentre research ethics committee
MSE	Mean square error
MTD	Maximum tolerated dose
MZ	Monozygotic
NI	Nonignorable (or noninformative)
NMB	Net monetary benefit
NNH	Number needed to harm
NNT	Number needed to treat
NPV	Negative predictive value
NRES	National Research Ethics Service
NRR	Net reproduction rate
OLS	Ordinary least squares
OR	Odds ratio
PCA	Principal component analysis
PDF	Probability density function
PEST	Planning and Evaluation of Sequential Trials (software)
PGM	Patient generated measure
PH	Proportional hazards
PK/PD	Pharmacokinetics/pharmacodynamics
POP	Persuade-the-optimist probability
PP	Per protocol
P-P	Percentile–percentile
PPP	Persuade-the-pessimist probability
PPV	Positive predictive value
QALY	Quality adjusted life-year
QoL	Quality of life
Q-Q	Quantile–quantile
QTL	Quantitative trait loci
RCT	Randomised controlled trial
REB	Research ethics board
REC	Research ethics committee
REML	Restricted maximum likelihood
ROC	Receiver operating characteristic
ROI	Region of interest
RPW	Randomised play-the-winner
RR	Relative risk
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean; structural equation model
SMR	Standardised mortality ratio
SPM	Statistical parametric map
SPRT	Sequential probability ratio test
SS	Sum of squares
SSE	Sum of squares due to error
SVM	Support vector machine
TDT	Transmission distortion test
TFR	Total fertility rate
TSM	Tree-structured method
TT	Triangular test
VAS	Visual analogue scale
WLSE	Weighted least squares estimate (or estimation)

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