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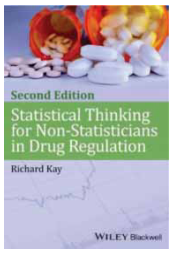

Statistical Thinking for Non-Statisticians in Drug Regulation (Second Edition)
By John Wiley & Sons, 2014. ISBN: 978-1-118-47094-7 (hardcover). 59.99 GBP. 368 pages.

George Bernard Shaw is believed to have said that *'It is the mark of a truly intelligent person to be moved by statistics'*, and it is clear from this book that author Richard Kay is such a person.

In 2014, this well-known lecturer and consultant to the pharmaceutical industry released a second edition of *Statistical Thinking for Non-Statisticians in Drug Regulation*. This book provides a comprehensive overview of statistical methods used within clinical drug trials and is targeted towards readers with a basic understanding of statistics and trial design. It will be beneficial to a range of non-statistician professionals in the clinical trial field, including but not limited to medical writers, data managers, programmers, and investigators. As a medical writer, I found this book particularly useful to both strengthen my current understanding of statistics and introduce new and unfamiliar terms.

The book is well-structured, with successive chapters giving the reader a step-by-step introduction to statistical procedures used in clinical trials. For this reason, I recommend that the book be read cover-to-cover, as many sections in later chapters refer back to earlier chapters. The author has clearly tailored the content well and, where necessary, each chapter is accompanied by relevant sections of the International Conference on Harmonisation (ICH) E9 guidelines, EMA guidelines, FDA guidelines, or Committee for Medicinal Products for Human Use (CHMP) guidelines, which help to present the statistical procedures from a regulatory standpoint.

The author has divided the book into 21 chapters. Chapters 1 through 4 introduce the reader to concepts including the use of control groups, placebos and blinding, randomisation strategies, sampling, the normal distribution, and the pitfalls of ensuring reduced error, before focusing on some of the basic statistical tests. Although a seasoned medical writer may find the content of these chapters all too familiar, it is a useful refresher to some of the fundamentals of trial design.

Chapter 5 has been restructured from the previous version and is now titled '*Adjusting the analysis*'. This chapter looks at why investigators might want to adjust an analysis due to imbalances in baseline factors such as age and explains that without such adjustment the means of two datasets may not be directly comparable. Methods described include two-way analysis of variance for continuous data and the Cochran-Mantel-Haenszel test for binary categorical and ordinal data. This chapter also discusses how to evaluate treatment homogeneity and the benefits of multi-centre trials. Chapter 6 extends chapter 5 by discussing how to adjust for several factors simultaneously with the use of simple, multiple, and logistic regression and analysis of covariance. Chapter 7 introduces the reader to the types of population analysis in trial design, focusing on the intention-to-treat (ITT) population and the per-protocol population. This chapter highlights the dangers of compromising the randomisation of patients at the analysis stage and the importance of using the ITT analysis (or full analysis set) to ensure the statistical comparison remains valid. It also discusses how to deal with the '*missing data*' caused by patients who fail to complete the study in line with the protocol. These approaches include but are not limited to: (1) Complete case analysis, (2) Last observation carried forward, (3) Success failure classification, and (4) Worst-case/best-case imputation. Each approach is accompanied by relevant guidance from ICH E9, the FDA, and the CHMP. Chapters 8 and 9 discuss further basics of clinical trial statistical considerations such as the importance of power and sample size in preventing type I and II errors and how statistical significance relates to clinical significance.

In the second half of the book, chapter 10 looks at how to deal with, and the regulatory view regarding, multiplicity or multiple testing, which occurs when a trial has multiple endpoints, multiple comparisons of treatments, or multiple subgroup comparisons. Such cases may require methods of adjustment such as Bonferroni correction, Hochberg correction, or interim analyses. Chapter 11 explores the advantages and disadvantages of using non-parametric tests when parametric tests are not applicable and discusses examples such as the Mann-Whitney U test and Wilcoxon signed-rank test.

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From a hypothesis perspective, clinical drug trials are broadly divided into three categories: superiority, equivalence, and non-inferiority. Chapter 12 focuses more on equivalence and non-inferiority studies, including how to define confidence interval (CI) margins and the need to use two-sided CIs for equivalence studies and one-sided CIs for non-inferiority studies. Chapter 13 looks at the analysis of survival data, including considerations for censoring, Kaplan-Meier curves, event rates, the use of median instead of mean survival, and constant and non-constant hazard ratios. This chapter extends chapters 6 and 8 by discussing adjusted analyses and sample size in the context of survival data and would be particularly useful for writers who work predominantly on oncology trials. Chapter 14 discusses the use of interim analyses and provides useful guidance on being compliant with data monitoring committees (DMCs).

In addition to the restructuring of several chapters, this second edition sees the addition of five new chapters: 15, 16, 17, 19, and 20. Chapter 15 focuses on Bayesian statistics and compares this methodology with classic and frequentist methods. It also introduces the concepts of prior and posterior beliefs, their role in Bayesian statistics, and the viewpoint of regulatory authorities on their use. Chapter 16 discusses adaptive designs, where aspects of a clinical trial can be changed based on accumulating data. This chapter also describes how to minimise bias in these designs and maintain the validity of the results. It further discusses various types of adaption and describes the regulatory guidance regarding the use of adaptive designs in exploratory and confirmatory studies.

Non-randomised (observational) designs offer an alternative to the '*gold standard*' of randomised controlled trials, but should only be considered when prior belief in the superiority of the test therapy is extremely strong and where the disease course is highly predictable. Chapter 17 focuses on non-randomised designs, discussing the types of bias they are affected by, such as selection, attrition, detection, and performance bias, and the regulatory guidelines concerning their use. Chapter 18 looks at the statistical considerations of meta-analysis such as methods of combination, CIs, and detecting heterogeneity. This chapter has been restructured since the first edition to include additional statistical methodologies, a case study example, and further regulatory aspects.

Chapter 19 looks at the various aspects of safety data analysis and the role of DMCs, including quantification of the benefit-risk balance for regulatory submissions. It also explains the importance of pharmacovigilance and the use of proportional reporting ratios in evaluating safety signals. Chapter 20 looks at statistical methods for evaluating diagnostic methods, including the use of receiver operating characteristic curves, regression models, and method comparison (e.g. use of the *kappa* statistic to measure agreement between two diagnostic tests).

The book concludes with chapter 21, which discusses the role of the statistician in designing trials and the essential role statistics plays in ensuring that a trial remains unbiased and provides valid results from which to draw meaningful conclusions.

In summary, this book gives a well-structured overview of the statistical procedures used in clinical trials. Statistics is not an easy subject to comprehend; most writers will have a basic understanding, but the relevance and the rationale behind the choice of statistical procedures may often be overlooked. In this book, the author has taken a complex subject and produced an invaluable resource that is straightforward to follow. The content and structure of the book provides a step-by-step overview of the design process; complex terms are well defined, and the abbreviations list, comprehensive reference list, and index add to the ease of understanding. Furthermore, the principles discussed in this book are applicable to a range of professions in the clinical trial field and numerous therapeutic areas. I would strongly recommend this book to any medical writer who compiles clinical study reports or clinical manuscripts on a regular basis.

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Writing for Science Journals: Tips, Tricks, and a Learning Plan
By Geoff Hart , Diaskeuasis Publishing, 2014, ISBN: 978-1-927972-01-4 (paperback). 22.00 GBP. 639 pages.

Most of us will be familiar with the sensation of sitting down to write in a new area with a blank page on the desk and a host of unformed questions that crystallise into 'How do I begin …?'

If that new area is manuscript writing, reading *Writing for Science Journals* (available in paperback,

e-published, and pdf versions) is a good beginning. This guide to writing for journals is subtitled 'Tips, Tricks and a Learning Plan' and presents the entire process of planning, preparing, writing, revising, and publishing a paper in a peer-reviewed science journal.

Geoff Hart is a Fellow of the Society for Technical Communication and has worked as a scientific editor for more than 25 years. He estimates to have edited more than 6000 works. He has helpfully distilled his experience into this book, including what he refers to as 'dirty secrets'–the inside knowledge on how papers are reviewed and assessed for publication. Although the book is evidently addressed to research students, there is plenty of information here to benefit medical writers.

Writing for Science Journals has 24 chapters that describe the entire manuscript writing process. Chapter 1 is an introductory chapter. Chapter 2 covers ethics and Chapter 3 covers choosing a journal. Chapter 4 discusses the outline of the manuscript (see below). Chapter 5 covers using a word processor. Chapters 6 to 13 cover the different sections of the manuscript in detail, after which Chapter 14 addresses experimental design and Chapter 15 explores numerical and statistical considerations. Chapters 16 and 17 cover figures and tables, respectively, and Chapter 18 covers online supplemental material. Chapters 19 and 20 address writing format and style. Lastly, Chapters 21 to 23 cover the process of review and publication, and conclusions are offered in Chapter 24.

Hart advocates the use of a strong outline (Chapter 4). He says 'it is difficult to review an entire manuscript, but easier and faster to review a short list of concise points to confirm that each is clear and that their sequence effectively tells your story'. Rather than take the journal article section headings and attempt to fill in a plan under them, Hart suggests summarising the following for the outline:

- 'The problem I investigated
- What questions remain unanswered
- Which of those I tried to answer
- Methods developed by previous researchers that I will use in my research
- New methods that I developed to solve problems other researchers did not solve
- Details of the statistical analysis required by my methods'

He explains that by extending this rationale to the plan for the results and discussion sections, one can ensure that 'each result in the results section has a method used to produce that result, and that every key interpretation in the discussion is supported by data described in the outline of the results section'.

In my view, this outline could be used as a check for much of the work that we do, as it can be all too easy to get distracted from the fundamental purpose of the research by the details of it. As with all the chapters, Hart uses examples throughout to illustrate his points.

The subsequent chapters on the sections of a journal article each finish with a summary of learning points. The style is narrative and approachable, with tips, notes, and asides. The chapters on experimental design (including how to choose a standard of comparison, how to eliminate bias, and how to replicate results), numbers and variables, figures, and tables contain a host of useful information that provides food for thought. Hart emphasises that there is considerable variation among journals; the guidelines in this book are delivered with the caveat that there should be thorough research into the specific requirements of the journal that you wish to target.

To some extent, information can feel hard to find. A note on the use of abbreviations is buried in Chapter 7 ('The First Pages'), whilst acronyms are dealt with in detail in Chapter 9 ('Materials and Methods'). It is also true that some chapters should be little needed by the medical writer (Chapter 5, 'Using Your Word Processor Efficiently', for example). However, read as a whole and using the index to navigate back to points of interest, this is an approachable and entertaining manual. Most interesting for me is that by being directed towards research students, the book provides awareness of the context of research writing outside of the medical writer's office. This, together with the clearly presented strategy for constructing a paper, makes this book well worth consulting.

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