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"Fundamental Concepts for New Clinical Trialists"

Scott Evans and Naitee Ting, 2015, 348 pages, CRC Press, $79.95

Review by Norman M. Goldfarb

"Fundamental Concepts for New Clinical Trialists" clearly and compactly covers the core scientific concepts of designing, data monitoring, analyzing, and reporting. It includes a lot of statistical content (*sans* formulae) for non-statisticians and encourages investigators to engage a statistician to be a key member of the study team:

> A typical image of the statistician is that of a data analyst, performing sample size calculations, and calculating p-values and confidence intervals. They are often viewed by other researchers as technicians, methodologists, mathematicians and programmers. However, clinical trial statisticians are collaborative strategists and experts in decision-making under uncertainty. The roles of statisticians have evolved into strategic and leadership positions, as the value of critical statistical thought has been realized by the research community. The roles of the clinical trial statistician have expanded to that of a scientist, researcher, teacher, student, consultant and communicator.
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> As well-rounded scientists who have intricate knowledge of the quantitative and conceptual issues, statisticians can make important contributions to all facets of a clinical trial. In fact, it is critical that statisticians be involved in many aspects of a clinical trial in order to optimize the scientific contributions of the trial and to avoid common pitfalls in a clinical trial development. Statisticians will soon realize that they must educate their research colleagues regarding the contributions that they can make throughout the life of a clinical trial. H.G. Wells once wrote, "Statistical thinking will one day be as necessary for efficient citizenship as the ability to read and write." While the world may be gradually moving toward this lofty vision, it is clear that statistical thinking is critical for efficient research.
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> The value of statisticians in clinical trial methodology research is showcased when statisticians create efficient designs, avoid potential pitfalls with intelligent foresight, and apply creative data monitoring techniques that allow for faster identification of efficacious or futile products while maintaining trial integrity. The FDA's increased rigor of statistical reviews has also highlighted the need for proper statistical input into clinical trials.
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> Statisticians can contribute immensely to the design of a clinical trial. Since the design of experiments and clinical trials is often taught in statistics and biostatistics departments, it only seems natural that statisticians play a lead role in trial designs. Unfortunately, some organizations do not capitalize on the skill of qualified statisticians to help direct the design of clinical trials, viewing statisticians' contribution as occurring only at the end of the trial when statistical analyses are needed. This often results in inefficient designs and trials that are unable to answer the research question of interest. Statisticians can help ask important questions, such as, "What is the appropriate control group?" "What are the assumptions of a specific design?" or "What is the appropriate endpoint?" They can help construct objectives to be precise, clear and phrased such that an associated hypothesis can be tested or a quantity (e.g., the treatment effect) can be estimated. Optimally, statisticians should take a lead in developing the design of a trial, ensuring that the design is the most efficient to achieve the study objectives.

Careful attention should be paid to potential sources of bias and confounding, as the optimal place to control for these problems is in study design. Variation in responses should be minimized as much as possible in order to identify treatment effects if they exist. The design may have associated assumptions that serve as a guide for the analyses to be performed and, thus, affects the interpretation of trial results and associated limitations. Statisticians understand these issues and, therefore, need to play a role in educating research colleagues with respect to such assumptions and limitations. Possible outcomes, interpretations and limitations can be conveyed prior to initiation of a clinical trial so that the interpretation of trial results is transparent, and unpleasant surprises can be avoided.

Every well-designed clinical trial has a clear protocol and a statistical analysis plan (SAP). Statisticians are the primary authors of SAPs and contribute to writing sections of the clinical trial protocol. Statisticians typically develop randomization methods, help decide if stratification is beneficial and feasible, [determine] if blinding can be achieved, contribute to the selection of an appropriate control group, decide on the choice of a target population, select endpoints and objectives, and construct sample size estimates for appropriately powering a study. Inexperienced statisticians frequently err by only reviewing the statistical section of the protocol. As integral members of the research team, statisticians should read and review the entire protocol and associated documentation for a clinical trial. Statisticians may not understand all the details of the clinical sections, but they should understand the basic concepts of each section.

Statisticians play a lead role in data monitoring (not to be confused with clinical monitoring at sites) of an ongoing clinical trial. Statisticians should develop a monitoring plan (MP) that outlines how the study will be monitored (e.g., what reports will be produced during the conduct of a trial, who will prepare and receive them, the contents of the report, and when the reports will be prepared). Statisticians should discuss the potential safety concerns with the project clinician and medical officer to determine how frequently interim analyses are required and what data will be important to review. Statisticians lead the preparation of the interim analysis reports for Data Monitoring Committees (DMCs) and present interim results at DMC meetings.

Statisticians are most recognized for conducting data analyses. Notably, the preparation for analyses begins in the trial design stage, and details regarding analyses are documented in a SAP developed by the protocol statisticians. The work culminates with the statistician helping to write a final study report and presenting the results to collaborating team members.

After an analysis is conducted, statisticians should play a central role in the overall interpretation and reporting of the data. Since the statistician has expertise and knowledge of the assumptions, limitations and interpretation of the statistical methods that have been applied, it is important that statisticians take a lead role in the interpretation of the data and help other researchers interpret the data and avoid overinterpretation of the data by optimistic researchers.

The book consists of 10 chapters:

- Clinical Trials
- Product Development Process
- Regulatory Review Organizations
- Clinical Trial Statisticians
- General Considerations in Clinical Trial Design

- Clinical Trial Designs
- Interim Data Monitoring
- Analysis Considerations
- Analysis of Safety, Benefit:Risk and Quality of Life
- Publishing Trial Results

The book is available in bookstores.

Reviewer

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.