JOURNAL OF CLINICAL RESEARCH BEST PRACTICES

Vol. 12, No. 12, December 2016 "Happy Trials to You"

"Multiregional Clinical Trials for Simultaneous Global New Drug Development"

Joshua Chen and Hui Quan, editors, 2016, 353 pages, CRC Press, $99.95

Review by Norman M. Goldfarb

"Multiregional Clinical Trials for Simultaneous Global New Drug Development" is essential reading for any clinical development executive contemplating a global trial, along with the managers tasked with conducting such a complex endeavor. While MRCTs can offer significant efficiencies (vs. a separate trial in each country), they definitely require a go-into-it-with-your-eyes-open attitude.

This book has been selected for

The First Clinical Research Bookshelf

Essential reading for clinical research professionals

The introductory section in the chapter on assessing the consistency of treatment effect across countries in an MRCT illuminates just some of the challenges:

> As randomized clinical trial (RCT) programs have increasingly become more global geographically, numerous challenges have resulted. One issue that arises with such global programs is the sometimes differing regulatory advice or requirements on primary or secondary endpoints. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has recognized this with the ongoing development of ICH E17 guidelines on the general considerations for the design of multiregional clinical trials. It is largely a function of the inexact science of medicine that health authorities with diverse healthcare systems do not always agree on which endpoints should be primary to evaluate a patient's response to a treatment for a specific disease, and therefore for a specific treatment development program. Even when there is agreement on the clinical measurement, there may not be agreement on the specific details in defining or analyzing that endpoint.
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> For example, regulatory authorities in one region may prefer a patient-reported outcome for a specific therapeutic area program, whereas authorities in another region may accept only a clinical outcome. In some cases, health authorities completely disagree on endpoints for a therapeutic area, whereas for other therapeutic areas, there may be agreement on the endpoint but differences in the appropriate time point to assess the endpoint, and/or the analysis approach for that endpoint. Such diverse views by health authorities on endpoints add significant complexity to the planning of global RCT development programs.
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> Among other potential differences, endpoints preferred by health authorities may differ in terms of the primary time point for hypothesis evaluation, the experimental designs for the RCTs, the noninferiority margins (or even if a noninferiority margin is necessary), and the specific comparator/dose for the RCTs. For general safety concerns, different health authorities often have different requirements for cumulative exposure to a test product in a filing. Another issue may arise when certain endpoints preferred by health authorities differ, but these differing endpoints are included in an RCT to help satisfy all health authorities; the endpoints may adversely affect the independent assessment of each other. For example, when one

endpoint is observed before another, the way a patient is treated may be impacted, and this impacts any other endpoints that can occur later in the trial, potentially impacting the integrity of other endpoints in the eyes of the health authority that puts most emphasis on those endpoints. Plans should be made to avoid unblinding and bias in such cases. Such plans, which may include using an independent unblinded third party to analyze the data, should be clearly described in the protocol.

Different views by health authorities on the appropriate experimental design for RCTs within a specific therapeutic area can be challenging to handle, depending on the magnitude of the differences. Clearly, minor regional differences could be simply described in the protocol, along with the analytic approach to handling such differences. However, major differences in experimental design, such as adding or using different treatment arms for specific regions, or different doses for different regions, can be very problematic. In some cases, resolution of these differences may only be satisfactorily addressed through separate trials.

In active comparator RCTs, where the goal is to show noninferiority instead of superiority, health authorities in different regions may prefer different noninferiority margins, or even different comparators. This can potentially lead to different, but spurious, conclusions of the same RCT for different regions. Establishing an appropriate noninferiority margin is critical for such RCTs, and the margin should be harmonized across regions, where possible. It is recommended to discuss the potential regional differences with all health authorities to gain agreement on a single margin. The single margin should be the most scientifically valid estimate, and not merely default to the most conservative margin. Defaulting to such a conservative margin would lead to an unnecessarily large study, requiring more subjects and investigators' time than would be necessary. Moreover, a trial that is unnecessarily large could raise ethical issues, besides potentially extending the time for the study to complete, which could delay the availability of a new effective drug to patients worldwide. The corollary is that negotiation of more efficient approaches takes time, may delay a product development program, and can be unsuccessful.

Health authorities may disagree on the appropriate patient population for a global product development program, which has implications for labeling by region. The preferred analysis population, such as intent to treat, full analysis set (FAS), or per protocol (PP), can vary by region. Often, analysis of both FAS and PP is done, and if there is disagreement, a discussion ensues on why such disagreement may exist. Similar results from these analysis populations are reassuring. The RCT protocol should clearly describe where differences between health authorities in different regions exist in terms of preferred analysis population and prespecify how analyses will proceed for these different regions. It may be necessary in such cases to describe the results separately by region to address the differences in analysis populations and the impact on results.

The book includes 26 chapters by 42 contributors:

- The Journey to Multiregional Clinical Trials in Support of Simultaneous Global Product Development
- General Principles and Considerations in Multiregional Clinical Trials for Simultaneous Global New Drug Development
- Bridging Studies versus Multiregional Trials
- Multiregional Clinical Trials: Assessing Consistency of Treatment Effect
- Regulatory Perspectives: Different Requirements/Endpoints and Needs for Harmonization

- Intrinsic and Extrinsic Factors and Rationales to Be Considered When Defining Regions
- Models and Sample Sizes for Multiregional Clinical Trials
- Multiregional Clinical Trials in Oncology Drug Development
- A Few More Considerations in Multiregional Clinical Trials
- Optimal Multiregional Clinical Trials
- Implementation of Multiregional Clinical Trial Design
- Independent Data Monitoring Committees in Multiregional Clinical Trials
- Monitoring Regional Differences Based on Blinded Data in Multiregional Clinical Trials
- Adaptive Multiregional Clinical Trials
- Lessons Learned and Recommendations Regarding Multiregional Clinical Trials from a Well-Practiced Industry Statistician
- Quantification of Regional Treatment Effects for Multiregional Clinical Trials
- Multiregional Clinical Trials: Country-Specific Assessment
- Multiregional Outcome Trial for a Multivalent Human Papillomavirus Vaccine: A Case Study
- The Discrete Random-Effects Model — Assessing Benefit and Consistency of Treatment Effect
- New Drug Development Paradigms in China: Simultaneous Global Drug Development Program
- Special Considerations for Emerging Markets
- A Predictive Bayesian Approach to the Design and Analysis of Bridging Studies
- Multiregional Clinical Trial: A Japanese Viewpoint
- Special Considerations for Medical Devices: An Overview
- Use of Multinational Randomized Clinical Trials in Economic Evaluations of Health Care
- Regional Benefit and Risk Evaluations

The book is available in bookstores.

Reviewer

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