THE PREVENTION AND TREATMENT OF MISSING DATA IN CLINICAL TRIALS

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SOURCE

Little RJ. et.al. 2012, "The Prevention and Treatment of Missing Data in Clinical Trials, New England Journal o f Medicine 2012; 367:1355-1360October 4, 2012DOI: viewed 10 October 2013, http://www.nejm.org/doi/full/10.1056/NEJMsr1203730.

INTRODUCTION

This review critically analyzes the article 'The Prevention and Treatment of Missing Data in Clinical Trials in the New England Journal of Medicine (NEJM). The review will summarize the article by providing the purpose for the article, how research was conducted, the results and other pertinent information from the article. The review will also critique the article analyze the article's accessibility and credibility based on its relevance to the subject matter. It will highlight some relevant progress in the topic under study that might have occurred since the article was published.

The article was well written, clear and relevant to the challenges facing the clinical research industry. Missing data points threaten the validity of many clinical trials. At the request of the Food and Drug Administration (FDA) and with its funding, the panel on the handling of missing data in clinical trials was created by the National Research Council's (NRC) Committee on National Statistics. This panel published a report with recommendations that was intended to be used by the FDA for guidance on handling missing data for the entire clinical trial community so that the latter can take measures to improve the conduct and analysis of clinical trials. The current article provides an overview of the findings and recommendations of the resultant report from the perspective of one member of the NRC panel.

Overall the paper succinctly summarizes issues related to missing data and the current state of challenges pertaining to the topic. It creates an understanding of the topic for the reader by discussing some of the main recommendations from the NRC panel's report on this topic.

ARTICLE SUMMARY

Consumers and stakeholders need reliable and evidence-based information for making health care choices. As stated earlier, Author RJ Little was part of the panel handling the issues with missing data in clinical trials. This article was part of the clinical problem solving series and has been well cited by others given that it is a very recent article.The purpose of the article was to provide a synopsis of the problem and the recommendations regarding the design, conduct, and analysis of studies to minimize that threat. The authors define missing data as "values that are not available and that would be meaningful for analysis if they were observed." They find that there is no analytic approach that can assuredly produce unbiased estimates of treatment effects when relevant data are missing and therefore recommendationconcludes that a more principled approach to design and analysis in the presence of missing data is both needed and desirable.Authors explored issues with missing data in clinical trial and aimed to document recommendations regarding 1) careful design and conduct to limit the amount and impact of missing data,(2) analysis that makes full use of information on all randomized participants based on careful attention to the assumptions about the nature of the missing data underlying estimates of treatment effects and 3) identified challenges and research gaps. Authors developed their methods based on the key steps suggested in the NRC Committee recommendations.

ARTICLE STRUCTURE

The article was divided into 6 keys sections. It was introduced with a background on how missing data compromises the inference drawn from clinical trials and went on to describe the key findings on how missing data in clinical trials can compromise scientific credibility and the need for sensitivity analysis. The paper then focused on proposing solutions and recommendations on limiting missing data in clinical trial from focus on trial design, planning, conduct follow through and analysis. The article was not based on conventional research study and therefore does not have the traditional sections expected in an article.

The article provides a synopsis on the recommendations from NRC on handling of missing data in clinical trials. The different sections in the paper are well defined, concise and yet narrative enough to draw deductions. The paper is not free from challenge, however, it does succinctly provides the readers an understanding on how the level of missing data can be reduced by creative approaches in the formulation of protocols design, study conduct, subject follow through, as well as in the selection and education of both investigators and patients. Authors did develop future research directions but did not wrap it up with a very well defined conclusion and therefore seemed to lack the closure in the main points. References were clearly cited in the literature section.

There were links to author and journals in the citations and references which allowed the reader to evaluate the articles more effectively. It also referenced the peer review letters which directed towards the critical analysis and feedback by the scientific community. The article also addresses all the members of the review panel and lists them under the source reference.

ARTICLE CRITIQUE

AUTHORITY

The article was published in the NEJM which is a peer-reviewed medical journal published by the Massachusetts Medical Society and is considered among the most prestigious in the world. The author's credibility was established by his PhD; the fact that the article was a peer reviewed article; the fact that the author is a distinguished professor of Biostatistics at the University of Michigan in the United States and has published well over 50 articles just in the area of missing data; the fact that the research described in the article was supported by FDA, (NRC) Committee on National Statistic, prominent universities across the globe and that the content of the article was part of the published report that was supposed to be used by the FDA for guidance on handling missing data for the entire clinical trial community. We are yet to see a clear guidance from the regulatory agency on this topic.

ACCURACY

At the time of the article there was little to no regulatory guidance on the design, conduct, and analysis of clinical trials and minimum specific advice on how to address the problem of missing data. In 2008 the FDA requested that the Committee on National Statistics convene a panel of experts in statistical approaches to handling missing data in clinical trials and analyzing results. The panel had multiple stakeholders, including clinical researchers, statistical researchers, appropriate experts from the National Institutes of Health and the pharmaceutical industry, regulators from FDA, and participants in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

From information obtained at the workshop and its deliberations, the panel prepared a summary of the workshop and a report with recommendations that was to become the basis of FDA's development of guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and appropriate statistical methods to address missing data for analysis of results. The source of the information in the article was based on some of the main findings and recommendations cited in the report by the NRC to address this gap. These scholarly and well informed sources and the endorsement from the clinical trial community lend accuracy to the information presented. Moreover, the strict editorial, references and sourcing processes also contributed to the article's accuracy as did the expert panel contributors from various disciplines around the globe.

CURRENCY

The journal was published in October 2012. The panel of experts started their deliberation end of 2008 and the program continued for about 15 months with a report produced by NRC in 2010. This article was written post NRC report on "The Prevention and Treatment of Missing Data in Clinical Trials. This article is fairly current and highlights a very relevant issue in the clinical trial arena that is constantly debated and deliberated on.

RELEVANCE

This article was published in a peer reviewed prestigious journal, which has high credibility in an academic context. It was written to inform researchers, regulators and industryand not meant for amusement, endorsement or publicity. It is relevant to all these groups and to the clinical trial industry as a whole. The article content is driven from the NRC's report and is highly relevant to the issues concerning missing data in clinical trials. It strives to identify ways in which FDA guidance should be augmented to facilitate the use of appropriate methods for controlling missing data by the designers and implementers of clinical trials.

OBJECTIVITY

The information was objectively developed, well supported with a current research base and with all evidence acknowledged and referenced. There was no evidence of bias, a fact that was reinforced by the recognition that the article documents decision from a panel of experts chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the report review committee of the NRC.

The fact that the article was based on was an independent review that provided candid and critical comments to assist the institution in making its published report. This independent review also ensured that the report met institutional standards for objectivity, evidence, and responsiveness to the study charge. Although the reviewers listed in the panel provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of the report was overseen by members that were appointed by the NRC's Report Review Committee.

These members were responsible for making certain that an independent examination of the NRC report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rested entirely with the authoring panel and the institution. Finally, the panel was supported by many federal agencies and through a grant from the National Science Foundation. The sheer meticulously cautious and independent review process lends credibility to the source of the article.

STABILITY

The article, with its source as apeer reviewed medical journal on an academic data base is stable as a resource. Also, the origin of the contents, endorsement by the medical, scientific and regulatory bodies qualifies the stability of the material discussed and the proposal recommended.

ANALYSIS OF TABLES

The article has no graphs, listings or figures. It has two tables, one highlighting ideas for limiting missing data in the design of clinical trials and other on conduct of clinical trials. By way of these tables and suggestions, Little et al. state that there is no easy fix for missing data at the analysis stage. Too many current analyses of clinical trials apply naive methods for missing-data adjustment that make unjustified assumptions, such as the last-observation-carried-forward approach. The handling of missing data requires a scientifically defensible analysis coupled with a sensitivity analysis to assess robustness. The key is to design and carry out the trial in a way that limits the problem of missing data.

Little et al. mention that limiting "the burden and inconvenience of data collection on the participants" as one of several ideas for limiting missing data in the conduct of clinical trials. Actually, critiques say that this idea should have been listed as one of the design feature. This would have not only helped limit missing data but also would have been important in limiting the burden on the investigators which is a critical factor in successful data retrieval as well as patient accrual.

Another feedback was that excessive data collection creates more opportunities for missing data. The best way to avoid missing data would be to collect minimal critical datathat relates to the overall research quality, patient safety and intervention efficacy.This concept is sometimes difficult to sell to investigators/industry who may envision ancillary studies and additional publications ensuing from more data. However, scientific community acknowledges that quality trumps quantity, and perhaps this should be made clearer in criteria for academic, scientific promotion.

Little and colleagues haveclearly stated that missing data are often the result of study designs that mandate study discontinuation when treatment is terminate. Intention-to-treat inference based on randomization requires that patient data be collected regardless of treatment status. However, according to peer reviewed feedback an issue that requires further clarification on is following patients who are off treatment, and methods used to address data that are missing at random. The authors proposed the idea to impute the results for those who have discontinued treatment based on the subjects who are following treatment seems to bechallenging. The goal should be to recreate a result that would have been obtained if patients who discontinued treatment had been followed. In addition, if the common practice of no longer considering data on patients after treatment discontinuation is not altered, methods to address missing data that are based on statistical models will have no similar patients from whom to model the missing data.

Overall the tables clearly outline the strategies for the design and conduct of clinical trials that will prevent missing data.

RECENT ADVANCES RELATED TO THE TOPIC

Missing data in research studies are the rule rather than the exception. Many reasons contribute to data missing from research projects. Whatever the reason(s) for missing data,their impact on quantitative research has been a great concern to methodologists.This topic has been the perennial topic in almost all facets of clinical trial design, conduct and analysis.An examination of articles published for the past year reveals that studies have incorporated design elements and

suggestions proposed by the NRC report into consideration however, there has been no official guideline from FDA regarding the missing data handling.

The two reports on handling of missing data endorsed by regulatory agencies are:

The prevention and treatment of missing data in clinical trials

• FDA-sponsored report by the National Research Council, published by the National Academy of Sciences (hereafter "FDA report")

Guideline on missing data in confirmatory trials

• European Medicines Agency (EMA), 2 July 2010

Other guidance that covers elements of handling missing data

Guidance for Industry and FDA Staff –"Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data"

• Sponsored by the U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) , May 2013 Drug Safety.

CONCLUSION

The content, structure, strengths and limitations of the article were analyzed and evaluated. The article has provided a synopsis on the NRC's comprehensive report and serves as the basis for the recommendations provided to FDA for development of guidance for clinical trials on appropriate study designs and follow-up methods to reduce missing data and appropriate statistical methods to address missing data for analysis of results. The article gave great insight into the future of prevention and treatment of missing data in the clinical trials and has scientific merits.

As stated earlier, there has been no official guideline from FDA regarding the missing data handling. It would be helpful for the scientific and clinical community if there was a guidance directed firstly to prevent missing data through changes in study design and subject follow-up methods, and second, to use appropriate statistical methods to deal with missing data in clinical trials.

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