The Prevention and Treatment of Missing Data in Clinical Trials: An FDA Perspective on the Importance of Dealing With It

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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 Committee on National Statistics. This panel recently published a report[1] with recommendations that will be of use not only to the FDA but also to the entire clinical trial community so that the latter can take measures to improve the conduct and analysis of clinical trials.

One of the FDA's reasons for seeking such a report was to develop recommendations that would contribute to a guidance for dealing with missing data in clinical trials and, wherever possible, for decreasing the extent of such missing data. A guidance would be directed toward the pharmaceutical industry, but we hope that it will be useful to the broader clinical trial community. The goal of such a guidance would be twofold: first, to prevent missing data, insofar as that is possible, 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.

This article is intended to share with a larger audience the importance of addressing the missing data problem in clinical trials, particularly the steps that may be taken to reduce the extent of missing data. The regulatory drug and biologics review process in the United States helps to ensure the quality of the clinical trials that will be submitted in support of marketing, and it provides a regulatory-science base to advance new methods, approaches, and innovations. Indeed, this is a large part of the FDA's mission.[2]

BACKGROUND

The randomized clinical trial, long the primary method of drug testing, relies on random assignment to treatments to remove potential bias in the estimation of treatment effects. The FDA's regulations on adequate and well-controlled trials and substantial evidence clearly articulate this point. Inherent in this principle, but not fully recognized until recent years, is the importance of being reasonably sure that when patients leave a study before the protocol-specified completion time (resulting in missing outcome data with respect to these patients beyond their respective withdrawal dates), the benefits of randomization have not been compromised—which could be the case if the withdrawals were treatment related and therefore not random. A classic remedy, at least in outcome studies, is to attempt to measure outcomes in all the subjects who were initially randomized, including those who withdraw from therapy; this is the "intent to treat" (ITT) approach to the analysis of clinical trial data. As an example of why this might be important, consider an outcome study (with an end point of survival) in which the test drug exacerbated heart failure. In these circumstances, subjects with heart failure, who might be at an increased risk for death, would be more likely to leave the test-drug group. This would lower the mortality risk in the test-drug group and give that drug an advantage with respect to its safety profile, unless the dropouts were followed and the post-dropout events counted. The ITT approach is intended to protect against this kind of "informative censoring" by requiring that dropouts be followed up and that post-dropout events be counted. It is recognized that an ITT analysis is conservative (after all, the benefits of a drug usually disappear once it is stopped), but this is generally considered acceptable in outcome studies. There are compromise approaches—e.g., counting events that occur within 30 days of stopping treatment, assuming that subjects are followed for that duration and it is possible to ascertain outcomes.

Trials of symptomatic benefit generally measure the effects of assigned treatment at successive visits over the duration of the trial, but they typically use the value measured at the final visit as the primary end point. In such trials, the missing-data problem is of a different kind. Early dropouts can leave treatment groups unbalanced with respect to important prognostic patient

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characteristics related to time-dependent response to treatments. The effect of these dropouts on outcome could go in either direction, i.e., exaggerating or minimizing drug–placebo differences, depending on the reasons for dropping out and whether there were spontaneous (i.e., not drug-related) changes in the outcomes in the study population. For example, if the population was improving spontaneously (a situation typical of trials in patients with depression), dropouts caused by adverse effects would disadvantage the drug group because the group would not show all the potential spontaneous changes over the full course of the study; conversely, dropouts from the placebo group because of lack of effect could exaggerate the drug treatment effect (**Figure 1**). On the other hand, if the population worsens over time, early dropouts because of adverse effects would favor the drug group in a last-observation-carried-forward (LOCF) analysis (**Figure 2**). Many ways to adjust for these early patient dropouts have been proposed, but there is no consensus on the best approaches. Also, the statistical methods used may not, in many situations, be able to satisfactorily estimate treatment effects without strong assumptions about reasons for dropouts and other factors that are not verifiable from the study data.

In symptomatic settings, it is not the usual practice to continue to assess effectiveness in patients after they have stopped taking the assigned treatment (ITT approach), as the drug's effect is assumed to be lost; also, in many cases, an alternative drug is started, and this could influence the outcome for a subject. It is also possible that if a serious adverse end point occurs after the subject has withdrawn from the assigned treatment that event is not captured in the study data. There is also generally less concern, in the symptomatic setting about not capturing a serious study endpoint that was about to occur.

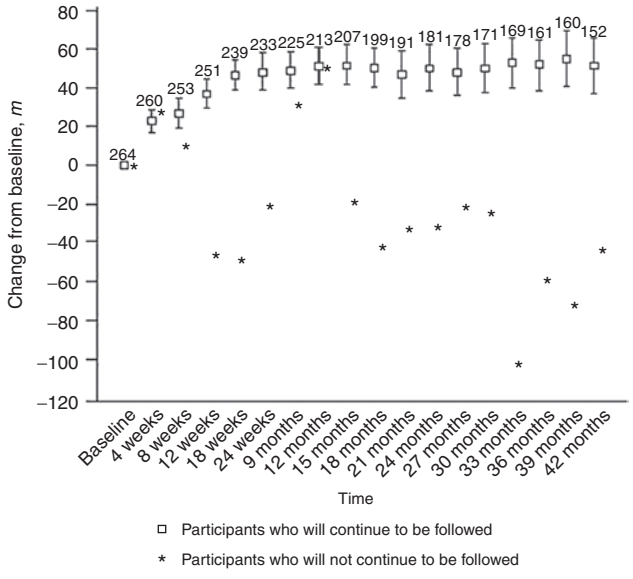

Figure 1 Change from baseline in 6-min walk distance over 48 months after initiation of treatment in patients with pulmonary arterial hypertension. At each scheduled visit, the average change from baseline in 6-min walk distance is plotted separately for the subgroups that will and will not remain under follow-up at the time of the next scheduled visit. The numbers above the squares represent, at each scheduled visit, the number of patients in the subgroup who will remain under follow-up at the time of the next scheduled visit. Hence, these are the numbers of patients whose data contribute to the calculations of the mean values and the 95% confidence intervals for that subgroup. Figure extracted from ref. 7.

The FDA reviews the protocols, patient data, analyses, and conclusions for all randomized trials that are submitted by sponsors in support of a claim of a new drug's efficacy. During almost 30 years of review experience, the issue of missing data in these clinical trials has been a major concern because of its potential impact on the inferences that can be drawn from the study. As noted, the problems can differ between outcome trials and symptom-related trials, but when data are missing in either kind of trial, the analysis and interpretation of the study pose a challenge and the conclusions become more tenuous as the extent of "missingness" increases.

The National Academy of Science (NAS) report[1] contains recommendations regarding minimizing the extent of missing data and dealing with missing data in analyses. The novel aspect of the report, which we emphasize here, is its focus on preventing missing data. Because it has long been thought that statistical methods can deal effectively with missing data, statisticians were often left to deal with the problem. The NAS report challenges that paradigm and encourages all parties to trials to find ways to minimize missing data.

THE NAS REPORT'S RECOMMENDATIONS

The complete list of the NAS panel's major recommendations is given in **Table 1**. The FDA has had a long-standing interest in addressing the problem of missing data, and the creation of the NAS panel reflected an attempt to deal with a persistent problem. Appropriately, the panel focused on phase III trials, which are intended to provide evidence of the efficacy and safety of new medical products. Possibly the most important observation by the panel was that the best approach to the issue of missing data was not analytic but tactical. The panel's first set of recommendations reflected its view that there is no best or only way to deal with missing data, nor is there any methodology that can recover the robustness and unbiased character of estimates derived from a complete set of data (with no data missing) after randomized allocation of subjects to study groups. Of course, this is not to deny that better or worse ways to deal with the missing data do

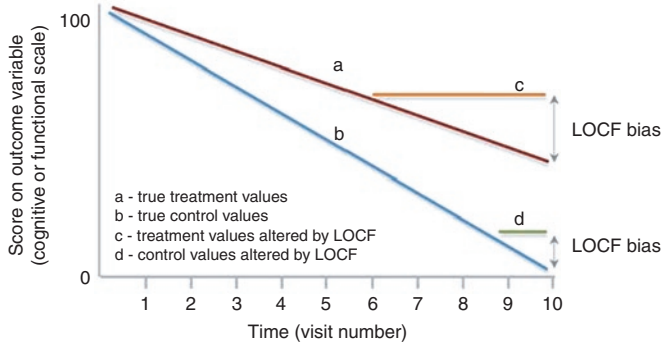

Figure 2 Differential last-observation-carried-forward (LOCF) bias when there are more or earlier dropouts in the treatment group than in the control group (effect measures by LOCF [c–d] > true effect [a–b], resulting in an exaggerated positive effect, biased in favor of treatment). Figure extracted from ref. 4.

Table 1 The 18 recommendations of the NAS report on missing data

1	The trial protocol should explicitly define (a) the objective(s) of the trial; (b) the associated primary outcome or outcomes; (c) how, when, and on whom the outcome or outcomes will be measured; and (d) the measures of intervention effects, that is, the causal estimands of primary interest. These measures should be meaningful for all study participants, and estimable with minimal assumptions. Concerning the latter, the protocol should address the potential impact and treatment of missing data.
2	Investigators, sponsors, and regulators should design clinical trials consistent with the goal of maximizing the number of participants who are maintained on the protocol-specified intervention until the outcome data are collected.
3	Trial sponsors should continue to collect information on key outcomes on participants who discontinue their protocol-specified intervention in the course of the study, except in those cases for which a compelling cost-benefit analysis argues otherwise, and this information should be recorded and used in the analysis.
4	The trial design team should consider whether participants who discontinue the protocol intervention should have access to and be encouraged to use specific alternative treatments. Such treatments should be specified in the study protocol.
5	Data collection and information about all relevant treatments and key covariates should be recorded for all initial study participants, whether or not participants received the intervention specified in the protocol.
6	Study sponsors should explicitly anticipate potential problems of missing data. In particular, the trial protocol should contain a section that addresses missing data issues, including the anticipated amount of missing data, and steps taken in trial design and trial conduct to monitor and limit the impact of missing data.
7	Informed consent documents should emphasize the importance of collecting outcome data from individuals who choose to discontinue treatment during the study, and they should encourage participants to provide this information whether or not they complete the anticipated course of study treatment.
8	All trial protocols should recognize the importance of minimizing the amount of missing data, and, in particular, they should set a minimum rate of completeness for the primary outcome(s), based on what has been achievable in similar past trials.
9	Statistical methods for handling missing data should be specified by clinical trial sponsors in study protocols, and their associated assumptions stated in a way that can be understood by clinicians.
10	Single imputation methods like last observation carried forward and baseline observation carried forward should not be used as the primary approach to the treatment of missing data unless the assumptions that underlie them are scientifically justified.
11	Parametric models in general, and random effects models in particular, should be used with caution, with all their assumptions clearly spelled out and justified. Models relying on parametric assumptions should be accompanied by goodness-of-fit procedures.
12	It is important that the primary analysis of the data from a clinical trial should account for the uncertainty attributable to missing data, so that under the stated missing data assumptions the associated significance tests have valid type I error rates and the confidence intervals have the nominal coverage properties. For inverse probability weighting and maximum likelihood methods, this analysis can be accomplished by appropriate computation of standard errors, using either asymptotic results or the bootstrap. For imputation, it is necessary to use appropriate rules for multiply imputing missing responses and combining results across imputed data sets because single imputation does not account for all sources of variability.
13	Weighted generalized estimating equations methods should be more widely used in settings when missing at random can be well justified and a stable weight model can be determined, as a possibly useful alternative to parametric modeling.
14	When substantial missing data are anticipated, auxiliary information should be collected that is believed to be associated with reasons for missing values and with the outcomes of interest. This could improve the primary analysis through use of a more appropriate missing at random model or help to carry out sensitivity analyses to assess the impact of missing data on estimates of treatment differences. In addition, investigators should seriously consider following up all or a random sample of trial dropouts, who have not withdrawn consent, to ask them to indicate why they dropped out of the study, and, if they are willing, to collect outcome measurements from them.
15	Sensitivity analyses should be part of the primary reporting of findings from clinical trials. Examining sensitivity to the assumptions about the missing data mechanism should be a mandatory component of reporting.
16	The U.S. Food and Drug Administration and the National Institutes of Health should make use of their extensive clinical trial databases to carry out a program of research, both internal and external, to identify common rates and causes of missing data in different domains and how different models perform in different settings. The results of such research can be used to inform future study designs and protocols.
17	The U.S. Food and Drug Administration (FDA) and drug, device, and biologic companies that sponsor clinical trials should carry out continued training of their analysts to keep abreast of up-to-date techniques for missing data analysis. FDA should also encourage continued training of their clinical reviewers to make them broadly familiar with missing data terminology and missing data methods.
18	The treatment of missing data in clinical trials, being a crucial issue, should have a higher priority for sponsors of statistical research, such as the National Institutes of Health and the National Science Foundation. There remain several important areas where progress is particularly needed, namely: (1) methods for sensitivity analysis and principled decision making based on the results from sensitivity analyses, (2) analysis of data where the missingness pattern is nonmonotone, (3) sample size calculations in the presence of missing data, and (4) design of clinical trials, in particular plans for follow-up after treatment discontinuation (degree of sampling, how many attempts are made, etc.), and (5) doable robust methods, to more clearly understand their strengths and vulnerabilities in practical settings. The development of software that supports coherent missing data analyses is also a high priority.

NAS, National Academy of Science.

From ref. 1.

exist, but by far the best course is to avoid the problem to the extent possible. This explains the title of the report and its strong emphasis on the prevention of missing data through better trial design and conduct. There were 18 recommendations in all, but here we focus on only a few of them, principally those related to decreasing the extent of missing data and on planning how to statistically analyze clinical trials that have problems of missing data. The specific analytic and statistical approaches (e.g., LOCF, modeling) will need considerable discussion as well as further analysis of their benefits and disadvantages in particular settings.

Recommendation 2 reflects the NAS's view of the best approach:

> Investigators, sponsors, and regulators should design clinical trials consistent with the goal of maximizing the number of participants who are maintained on the protocol-specified intervention until the outcome data are collected.

Recommendation 3 suggests more use of postwithdrawal data (to minimize missingness) and is potentially more controversial:

> Trial sponsors should continue to collect information on key outcomes on participants who discontinue their protocol specified intervention in the course of the study, except in those cases for which a compelling cost-benefit analysis argues otherwise, and this information should be recorded and used in the analysis.

Although such an ITT approach is reasonably standard and broadly accepted for outcome studies, it is not usual—and not clearly desirable—in studies of symptoms. In this category of studies, it is strongly expected that there could be a prompt loss of a drug's effect after it is discontinued; therefore, the inclusion of data from subjects who have discontinued the drug would introduce a bias against the drug when ITT analysis is carried out. Also, it is the common practice for dropout patients to switch therapies; this would further confound the results of the analysis.

Recommendations 6 and 9 call for more explicit attention to the entire problem of missing data, a step that would surely be beneficial for all aspects of the problem:

> Recommendation 6: Study sponsors should explicitly anticipate potential problems of missing data. In particular, the trial protocol should contain a section that addresses missing data issues, including the anticipated amount of missing data, and steps taken in trial design and trial conduct to monitor and limit the impact of missing data. Recommendation 9: Statistical methods for handling missing data should be specified by clinical trial sponsors in study protocols and their associated assumptions stated in a way that can be understood by clinicians.

The other recommendations in the report deal primarily with data-analysis proposals. They include a variety of statistical methods, some of them relatively sophisticated, and most of them not currently in routine use in clinical trial analysis. Of course, this situation could change. The report also advocates (recommendation 16) the development of new research on the issue of missing data and on analysis of existing large FDA databases of clinical trials to help define best practices for dealing with missing data. In particular, it seems especially important to learn how often results change when different methods of analyzing the data (LOCF vs. more sophisticated modeling approaches) are applied and whether this can be predicted from, for example, the causes of dropouts (adverse effect vs. lack of effectiveness) or the extent and timing of the dropouts. It also encourages (recommendations 17 and 18) a generally higher level of training in and attention to the wide range of problems resulting from missing data.

MINIMIZING MISSING DATA BY DESIGN

The report emphasizes that there are study-design improvements that can minimize the likelihood of missing data and makes some specific suggestions about how to do this. It describes a study design with particularly great potential for minimizing missing data: the randomized withdrawal study. Although this is not appropriate for all situations, and is not a complete substitute for more conventionally designed placebo-controlled trials, the randomized withdrawal study has important advantages in its approach toward minimizing postrandomization dropouts. In a randomized withdrawal study, patients who appear to have responded to and tolerated treatment in an open-label period or in the treatment arm of a randomized trial are randomized to either continued drug treatment or placebo. Because such trials generally involve only patients who appear to have responded, the study is enriched with apparent responders and with patients who are willing to remain on the test treatment. The randomized withdrawal study design was proposed by Amery *et al.*[3] in 1975 as a way to determine the long-term effectiveness of drugs without requiring a long-term placebo control treatment, given that the latter is not acceptable in many situations, e.g., for most psychiatric and antihypertensive drug treatments. This design is now standard when the objective is to demonstrate long-term blood pressure effects of antihypertensive drugs and to establish maintenance of effectiveness of a variety of psychiatric treatments (such as for depression and anxiety), for which reduced recurrence rates are the measures of effectiveness. The design can also be used as an initial trial to show effectiveness when there is an existing population of patients using the drug in an open treatment setting (e.g., with an investigational new drug or off-label use of an approved drug, which is not unusual in rare-disease settings).

As noted the randomized withdrawal design was developed as a more ethical way to establish long-term effectiveness, avoiding long-term placebo treatment in a randomized trial. Apart from concerns about such long periods of discomfort for patients, it is difficult to recruit and retain patients for trials with such long-term placebo exposure. Consequently, dropout rates are often high, contributing to the missing-data problem and posing difficulties during analyses. By contrast, in a patient population on treatment for 5 months, a withdrawal trial of a short

duration (2 weeks or 1 month) would provide evidence of prolonged effectiveness with only brief exposure to placebo and, in all likelihood, low dropout rates.

Another approach is to consider use of a shorter study or an earlier study endpoint than is currently used, perhaps supported by a randomized withdrawal study to evaluate the duration of drug effect. Studies of acute depression, for example, are typically of 6 weeks' duration and have as their primary end point the effect at 6 weeks, usually with some analysis of the many dropouts that regularly occur. The full effect of antidepressants, however, is usually observed by 3–4 weeks of treatment, and dropouts increase greatly after 4 weeks. Even in a planned 6-week study, if the primary end point were chosen as 4 weeks, there would be much less missing data with respect to the critical-effectiveness conclusion and the 6-week data could be examined secondarily. A similar approach could be considered for pain-related studies, in which subjects who withdraw from a study or do not complete the full assigned treatment regimen are also a significant problem. In these studies, it might be possible to first establish an acute effect (e.g., at 1 or 2 weeks), followed by a randomized withdrawal study in responders at, say, 12 weeks, to evaluate maintenance of effectiveness. A further advantage of such a design is that it measures continued effectiveness in subjects who had a response in the first place (why measure continued response in people who never responded?).

CONCLUSIONS

This brief commentary is intended to highlight the important concepts in the recent report by the NAS Panel on the Handling of Missing Data in Clinical Trials. The panel report[1] was requested by and funded by the FDA, but its recommendations were completely independent of FDA involvement. These recommendations will be of use not only to the FDA but also to the clinical trial community at large so that the latter can take measures to improve the conduct and analysis of clinical trials. It is expected that the report will help to change the current approaches to dealing with missing data.

Although it is clear that the problem of missing data in clinical trials is pervasive, it is not clear how the problem can be best addressed, and by whom. It is our view, consistent with that of the NAS report, that the most critical change required is a cultural shift in the way trials are conducted and managed, to focus on preventing the phenomenon of missing data. For this purpose, the report proposes modifications across a variety of areas. Implementing any of these changes will take time and require extensive consciousness raising in the clinical trial community. Despite improved efforts, there will surely continue to be some missing data even in well-conducted clinical trials, and the problem of dealing with this remains a critical issue. It has been suggested by Molnar and colleagues[4] that the current approaches to missing data in some areas of symptomatic treatment are, in part, a regulatory issue; indeed, some are of the opinion that the approaches required by regulators with respect to dealing with missing data (notably LOCF) are not optimal. In addition, the editors of the major medical journals have not, in our opinion, dealt with this issue adequately, as seen from the fact that the reporting on clinical trials in the literature usually does not address the issue of missing data in any meaningful way. Altman[5,6] has suggested that the CONSORT group could give guidance on methods for analyzing trials when data are missing, but he also points out that because the role of the CONSORT group is to give guidance on the reporting of what was done, and not to advise on what is good or bad methodology, CONSORT guidance cannot address critical parts of the issue. Given the great concern about the problems with LOCF analysis, however, it seems clear that both the regulatory review process and the drug development process will need to address the matter. All in all, the NAS panel's report on preventing and addressing missing data in clinical trials provides a roadmap, or perhaps a "problem list," for how we might proceed in the future. The FDA will use this report to help develop consensus on best approaches and identify areas that need more discussion; it hopes to develop guidance that will promote better design and analysis of trials while also reducing the uncertainty on the part of the people who design and conduct the trials.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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