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MISSING INACTION: PREVENTING MISSING OUTCOME DATA IN RANDOMIZED CLINICAL TRIALS

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Many methods are available to deal with missing data in randomized clinical trials, and active statistical research in the area continues. When, however, a high proportion of outcome data is missing, the methods can produce inaccurate estimates of the true effect size. This article argues that trialists should aim to minimize the proportion of missing data. To that end, the article suggests training investigators and study participants about the importance of completing the trial. It proposes language for informed consent documents, protocols, and case report forms that will distinguish between stopping study medication and removal from the trial itself.

Key Words: Completers analysis; Imputation; Last observation carried forward; Missing data; Multiple imputation; Randomized clinical trials.

1. INTRODUCTION: THE LATENT PATIENT

In the imaginary world of perfect randomized clinical trials, all randomized participants would follow the protocol without any violation and all would have a measured primary outcome variable. Well-run trials with all-cause mortality as the primary outcome variable often approach that ideal. In the VALIANT trial of all-cause mortality in patients with high-risk myocardial infarction, "study medication was administered to all but 77 patients (0.5 percent . . .). The median duration of follow-up was 24.7 months, for a total of 29,226 cumulative patient-years. At the completion of the trial, the vital status was unavailable for 139 patients (0.9 percent . . .), 55 of whom had withdrawn consent" (Pfeffer et al., 2003). In such a situation, the few participants with unknown primary outcome data have only trivial influence on inference regarding the effect of treatment. One need only show that all reasonable assumptions about the missing data produce quantitatively similar estimates of effect size. Even when participants withdraw consent from further participation, investigators may consult relevant public records (e.g., for survival status) (Good Clinical Practice Program, 2008). The problem of missing data becomes more difficult as the outcomes become more subjective and the proportion of missing outcomes increases. In cardiovascular trials with a composite outcome (e.g., cardiovascular death, myocardial infarction, or stroke) rather than total mortality, one can no longer rely on public records to determine

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the outcomes of those who become lost to follow-up, so the proportion of missing values may increase. If the treatment effect is strong, a set of reasonable sensitivity analyses can provide insight into the likely range of treatment effect. Notably, some cardiovascular trials with composite outcomes have admirable records of nearly complete follow-up. For example, in the ONTARGET trial, a three-arm trial of telmisartan, ramipril, or both in patients at high risk for vascular events, the primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Of the 25,620 randomized participants, "A total of 25,577 patients (99.8%) were followed until a primary event occurred or until the end of the study (median, 56 months)" (ONTARGET Investigators, 2008).

When the outcome variable is a clinical event, a missing value has a clear interpretation. The person whose outcome is unknown either did or did not experience the outcome. If the primary analysis of that outcome variable relies on its binary nature by using, say, a binomial or logistic model, the missing data present a practical, not a conceptual, problem. Sensitivity analyses that assign success or failure to missing values can provide a range of estimates and p values under a variety of assumptions.

If the statistical method requires an analysis of time to event, the sensitivity analyses become a little stickier because must one play with not only whether or not each missing participant experienced an event but also when that event occurred.

When, however, the outcome variable is a continuous measure, or a dichotomized variable from a continuous measure, or an outcome that may not occur because of a competing risk, the problem of missing values looms larger. First, trials of such measures often have a much higher percentage of missing values; 5% (Di Bisceglie et al., 2008), 30% (Jenkins et al., 2008), or even nearly 50% (Bezjak et al., 2008; Land, 2008) of participants may have missing data on the primary outcome variable. Table 1 shows the percentages of missing outcome data I have seen in various trials on which I have worked. In these cases, sensitivity analyses

Table 1 Extent of missing primary outcome data for typical trials

Disease	Length of trial	Outcome	Percent missing
Cardiovascular disease	Median follow-up ~2 years	Hard clinical outcomes (e.g., death, MI, stroke)	< 2%
Cancer	Median follow-up ~2 years	Progression-free survival	2–20%
Hypertension	12 weeks	Blood pressure	5–10%
Osteoarthritis	12 weeks	Patient-reported assessment of pain	20–40%
Schizophrenia	12 weeks	Positive and Negative Syndrome Scale (PANSS)	30–50%
Infectious disease	12 weeks	Cure	20–50%
Vaccine trial	2 years post last vaccination	Case of disease	10–40%

Note. These "data" come from the author's experience with many trials. The reader should consider them only as rough indicators of the extent of missing data in typical trials.

may not suffice because small changes in assumptions can lead to large changes in results.

Even more importantly, the question being addressed may become ambiguous. Suppose, for example, the trial is studying cancer and the outcome is progression. Suppose further that 20% of the participants die before they progress. What does it mean to ask about progressions in latent patients, that is, in the group of patients who died? Or suppose we are dealing with a 12-week trial of pain relief among patients with chronic pain. Imagine that 40% of the group stop medication and drop out of the study before reaching the 12-week assessment of pain. What does it mean to ask about the pain the drop-outs experience at 12 weeks? Are we asking about their actual, but unmeasured, level of pain at 12 weeks? Or the pain that they would have experienced had they continued on study medication? Or something else?

The statistical literature describes many methods for dealing with missing data, some quite sophisticated and useful; however, in this article I argue that unless we are involved in a trial with a small amount of missing data and clarity about what being missing means, we should be spending more effort than we do trying to prevent missing data. After a brief once-over-lightly of the methods in our armamentarium for dealing with missing data, I offer some conjectures to explain why our clinical colleagues seem much less bothered by missing data than we are. I then point out that our protocols often encourage, or at least fail to discourage, missing data. I end with some suggestions for preventing missing outcome data.

2. METHODS TO DEAL WITH MISSING VALUES: A ONCE-OVER LIGHTLY

This section briefly sketches the methods available to us to deal with missing data. It spends more time on the methods commonly used than on the more sophisticated methods that I think are, regrettably, less common. The examples come from recent published articles, mostly from 2008, to emphasize that the failure to deal carefully with missing data is not a relic of past behavior.

Probably the most common method investigators use to deal with missing data is simply to ignore the fact that some data are missing and analyze only the data that are available. The medical literature is full of examples of papers that report a so–called "completers" analysis that uses only the data at hand. For example, in a double-blind, placebo-controlled trial of efficacy and safety of thalidomide in AIDS-associated wasting, 103 male patients were randomized to thalidomide at 100 mg/day, 200 mg/day, or placebo for 8 weeks. The paper reported that 64 patients completed the 8 weeks of study treatment. Among these completers, both treatment groups showed significant weight gain compared to placebo (2.2 kg in the 100 mg/day group, $p = 0.008$ versus placebo; and 1.5 kg in the 200 mg/day group, $p = 0.019$ versus placebo) (Kaplan et al., 2000). While this paper also reported an analysis that incorporated all randomized participants, it focused primarily on the conclusions from the completers analysis. Thumbing through many medical journals will show completers analyses. While we statisticians frown on such completers analyses, or their analogue "adherers" analyses, because of the obvious bias they invite (Coronary Drug Project Research Group, 1980), such analyses are common in the literature even today. Smith et al. (2008) describe a randomized trial of a selective 5-HT(2C) agonist for the treatment of obesity. According to the authors,

"The primary end point was change in weight from baseline to day 85 by completer analysis."

Reliance on an analysis of completers assumes that the reason for missing is the same in both treatment groups and further that the patients who are missing data are a completely random sample of all those randomized. What we as statisticians fear is that those with data differ in some fundamental way from those without data, that the differences are related to the distribution of the outcome variable (if we could measure it), and that the differences between missing and non-missing differ by treatment group. While others find comfort when the proportion of missing data is the same in the treatment groups, we statisticians warn that just because the percentages are the same does not mean that the *reasons* are the same.

Another frequently used method, and one that the Food and Drug Administration (FDA) has recommended (but see, Food and Drug Administration, 2005, for a recommendation for LOCF tempered by some hesitation), is the last observation carried forward (LOCF) approach. This type of analysis is common in studies of chronic conditions such as pain, psychiatric disease, and Alzheimer's disease. The underlying philosophy behind LOCF analysis must be the assumption that a person who stops study medication, our "latent patient," would have had a constant value of the outcome from the time of dropout to the time of the last scheduled visit had that person continued study medication. A recent example of this type of analysis comes from a study published in 2008 that assessed the drug dimebon in 183 patients with mild to moderate Alzheimer's disease. The primary outcome measure assessed change in cognition from baseline to week 26. The authors state, "We compared dimebon with placebo with an intention-to-treat analysis, with last observation carried forward (ITT-LOCF) imputation" (Doody et al., 2008).

The examples just presented illustrate two common ways randomized trials deal with missing data: either ignoring the missing data or imputing missing values by LOCF. Other methods of imputation are also in use. For binary variables, several simple methods are available for imputing data. In some trials, missing values are imputed by assuming that people with missing observations would have experienced the same rate as the completers in their group. This neat trick has the effect of rewarding investigators for having missing data because the effective sample size, relative to what is observed, increases while the effect size remains the same. Imagine, for example, a study of 80 participants, 40 in each group, with 20 successes in the treated and 12 in the control group. The p value from Fisher's exact test comparing these two percentages would be 0.11. Now imagine that the study really had randomized 120 participants, 60 in each group, but 20 in each group were missing. The imputation method that assumes the missing observations share the rates of the observed data would calculate successes in 30 in the treated group and 16 in the control group; the estimated proportions would be unchanged, but the p value would now be 0.040. Thus, in the face of more uncertainty, this method adds false precision.

Other methods of simple imputation would assign everyone the rate in the placebo group or the rate in the opposite treatment group—that is, the patients randomized to placebo are assigned the rate in the treated group and the patients randomized to treatment are assigned the placebo rate (Proschan et al., 2001). Both of these methods of assignment lead to conservative estimates of effect size.

Some people use a true worst-case analysis by assuming that all in the treated group are failures and all in the treated group are successes. This method is very often unrealistically conservative. None of these methods reward a study for having missing values but all make somewhat arbitrary assignments. Multiple imputation (Rubin, 1987), which now can be implemented in SAS (SAS Institute, Inc., 2006), is a more elegant approach, but it too requires assumptions that may not be realistic.

An analogous class of methods is available for continuous outcomes (i.e., completers, LOCF, multiple imputation). In addition to the approaches that ignore the missing data or that carry the last observation forward, some studies carry the baseline forward on the grounds that if a person stopped taking study medication, the value of the outcome of interest would likely revert to what it was at baseline (see, for example, Jenkins et al., 2008). Some methods impute missing values by using the mean value in their own respective group, some use the mean in the combined group, some the mean in the placebo group, and some the mean in the opposite group. Some use the preceding ideas but use ranks rather than the values themselves. And, again, if we have a reasonable model, multiple imputation may be useful. Still another approach, the "continuous responder" method, allows a flexible approach to dichotomizing a continuous variable and thus comparing distributions on the basis of their cumulative distribution functions (Kim, 2007; Permutt, 2008).

For longitudinal data, we can once more ignore the missing observations or we can carry forward the last observation or the baseline observations. We can assume the missing observations follow their own group's trajectory, the opposite group's trajectory, or the placebo group's trajectory. For many situations, more defensible approaches are mixed models or carrying the last rank forward (O'Brien et al., 2005).

For survival data, the typical approach is to censor data when a person drops out of the study. Other possibilities are to assume that the dropout experienced an event at some time after dropout, and to assume the rate or event would be the same as the rate in the latent patient's group, in the opposite group, or in the combined group.

The methods described have various advantages, but all suffer some limitations. Perhaps most worrisome is, not surprisingly, that when many observations are missing, different analyses that on their face appear reasonable can produce very different results. Not only can the magnitude of the effect change, but the direction of the effect can change as well.

3. EVIDENCE THAT MANY OF OUR COLLEAGUES (AND MANY JOURNALS) FAIL TO AGONIZE ABOUT MISSING DATA

If clinical researchers, and clinical journals, worried as much about missing data as we statisticians do, the methods section of papers would routinely discuss how the investigators planned to deal with missing data, the text would report clearly the extent of missing data, and the tables and graphs would identify what data are measured and what are missing. All too often, however, ferreting out the amount and timing of missing data poses an insolvable challenge to the reader. Suppose, for example, a randomized trial that studied participants over 12 months compared two interventions with respect to visual acuity over time with monthly measurements of visual acuity. The typical graphical representation might look like Fig. 1, which shows the mean value of best corrected visual acuity (BCVA) over time. The reader might assume that each point on the graph represents values from

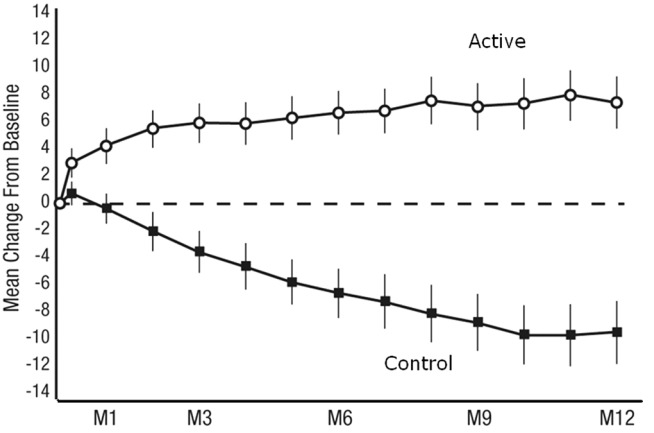

Figure 1 Mean change from baseline in number of letters read (best corrected visual acuity) over time. The graph shows a typical representation of a 12-month trial with monthly measurements. Note that the legend does not show the sample size at each point, so that even if the text tells the reader that the curves present LOCF data, nowhere does the graph or the text describe the number of observations that were in fact missing.

the same group of people; however, the text might tell the reader that missing data were imputed by LOCF. Nowhere in the text of the paper, nor on the graph itself, does the reader see how many measurements were actually taken and how many were LOCF-ed. (Even papers that deal carefully with missing data often do not show either in the graphs or in the text when participants dropped out; see, for example, Jenkins et al., 2008.)

The situation is often not much better with survival curves. Many survival curves fail to show marks indicating censoring. Even if censoring marks are present, the curves almost never show which observations were censored because the study ended, which because the patient died or experienced another competing event that precluded measuring the event of interest, and which because the patient dropped out of the study (e.g., Fig. 2).

Another indication that many investigators are not sufficiently concerned with how to handle missing data and how to interpret trials with missing data is the fact that very few papers distinguish in their analyses the reasons for stopping study medication. The person who stops because of "lack of efficacy" is quite different from the one who stops because of intolerability. While one can argue that LOCF may be reasonable for the former case if one assumes that the disease is not progressive, it hardly is so for the latter. The use of LOCF for a participant whose symptoms are improved by a drug but who cannot tolerate it is implicitly assuming a latent patient whose characteristics differ from those of the observed participant.

In some situations, dropping out of a study (or stopping study medication) may be a manifestation of the underlying disease. For example, the inability of a psychotic patient, or a demented one, to adhere to therapy may reflect not the inherent qualities of the treatment but the process of the disease itself. On the other hand, stopping study medication may result from improvement of symptoms either because the patient no longer feels the need for therapy or because, having

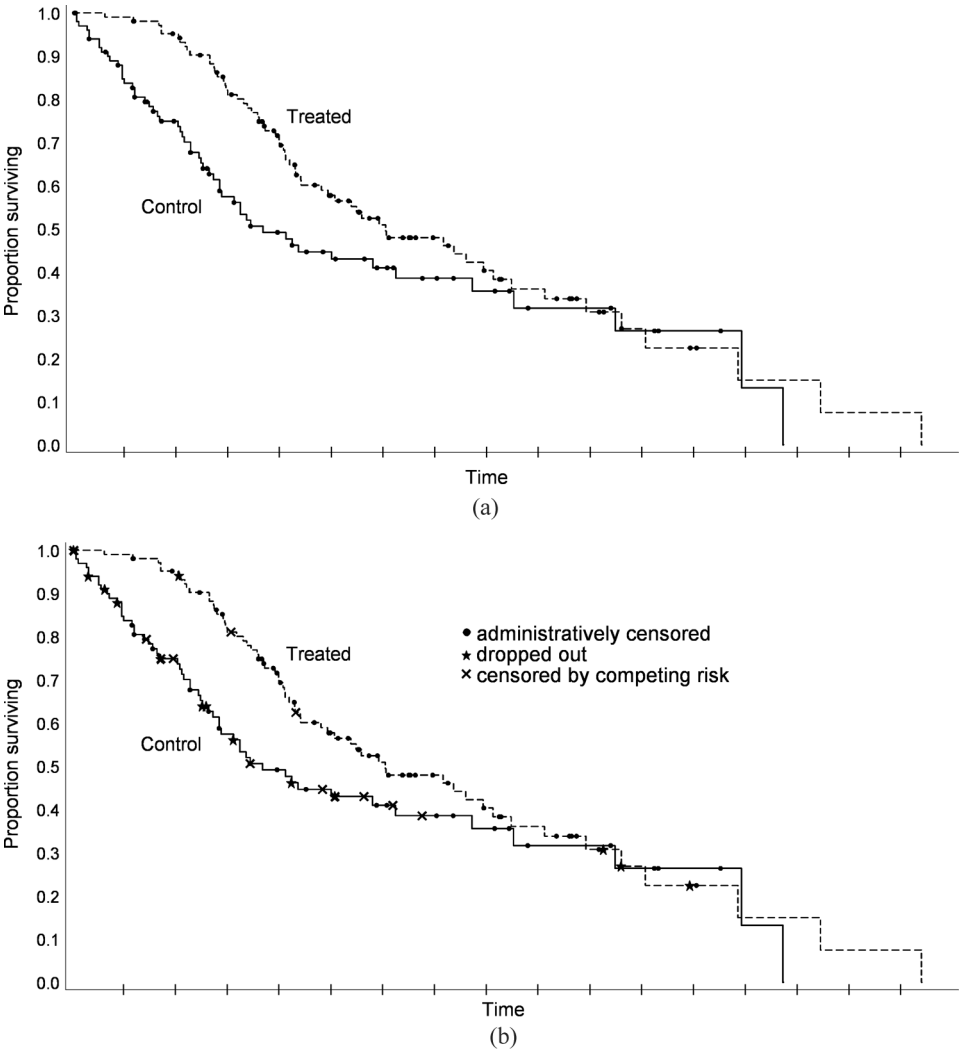

Figure 2 Survival curves. (a) Typical survival curves with times of censoring identified. These survival curves shows time to event. The curves do not show which censoring are administrative, which are drop-outs, and which are due to competing risks. (b) Suggested survival curves with reason for censoring identified. A comparison of (a) and (b) shows that while the total numbers of patients censored in the treated and control groups were approximately the same, the distributions of reasons for censoring differed considerably.

improved, the patient finds the side effects now become more intolerable than the condition the drug was designed to alleviate.

4. WHY DON'T THEY CARE?

If the manner in which papers report missing data indicates that many clinical investigators feel little angst about the extent of missingness, we statisticians need

to understand why. Only then can we effectively educate the community of clinical researchers and institute changes to help prevent missing values, or at least to report them more accurately.

In trials with a clinical event as the primary outcome variable, many investigators understand and abide by the principle of once randomized, always analyzed. (There are exceptions. For example, in many randomized trials in oncology when the outcome is progression-free survival, investigators censor people when they cross over to another therapy and then fail to follow participants for any subsequent outcome other than mortality.)

In trials of symptoms, however, or more generally trials with continuous outcomes, the attitude of many investigators is, "Why should I care what happens to people who stop taking the study medication?" Sometimes they express their opinion more dismissively: "I know the drug won't work if the patient is not taking it!" Or, they might be worried lest the comparison between treatment groups would be confounded by subsequent therapy. Implied in these comments is a failure to come to grips with the fundamental purpose of randomization—to produce groups of expected equal risk. Randomization is necessary, but not sufficient, to ensure valid comparisons—one needs not only randomization but analysis that truly reflects the randomization. If we had a method of reliably removing from the analysis set those in treatment group A who would have dropped out had they been assigned B and those in group B who would have dropped out had they been assigned A, then we could make the comparison between "adherers to A and B," but we have no such mechanism (except perhaps in very specially designed trials).

In addition to the conviction that only those who adhere are relevant to the assessment of a drug, investigators and sponsors often cite the difficulty and expense of having patients continue the visit schedule after they have stopped study medication.

5. HOW TRIALS DISCOURAGE FOLLOW-UP OF THOSE WHO STOP STUDY MEDICATION

The documents associated with many trials may discourage full follow-up of participants. This section quotes from typical informed consent documents, protocols, and case report forms, with suggestions for alternative wording that may encourage more complete follow-up.

The following language comes from an amalgam of informed consent documents.

> Participation in this study is entirely voluntary. Your treatment and your doctor's attitude toward you will not be affected should you decide not to participate in this study... You will be asked to return for follow-up visits and to provide follow-up information... If you agree to participate, you may withdraw from the study at any time without affecting any benefits to which you would otherwise be entitled.

Nowhere does the language of most informed consent documents describe the distinction between stopping study medication and withdrawing from the study itself. A small revision of the document would identify that distinction to the

potential participant. The investigator, in obtaining informed consent, should ensure that the potential participant understands the distinction.

> Participation in this study is entirely voluntary. Your treatment and your doctor's attitude toward you will not be affected should you decide not to participate in this study... You will be asked to return for follow-up visits and to provide follow-up information *even if you have stopped taking study medication. Your doctor will contact you to obtain follow-up information.* If you agree to participate, you may withdraw from the study at any time without affecting any benefits to which you would otherwise be entitled.

A permissive sentence often appears in the section on calculation of sample size (suggesting that statisticians themselves approved the message). A typical such sentence reads something like, "Ten percent (10%) of the subjects are expected to drop out; therefore the sample size has been increased by 10%." This sentence only makes sense if the planned analysis is a completers analysis; otherwise, the increase in sample size occasioned by a 10% drop out should be more than 10% to account for the increased uncertainty, and hence increased variance, that a rigorous analysis would entail. Lavori (private communication) suggests as a rule of thumb that a trial should offset every missing observation with three nonmissing values; thus, investigators who anticipate 10% missing should inflate their sample size by 30%.

Trials of symptoms or continuous outcomes make the requisite bow toward intent-to-treat ("The primary analysis will use the intent-to-treat population") followed by a set of exclusions ("The ITT population is defined as all those randomized who ..."). The protocol for an outcome trial may say, "The reason that a subject discontinues from the study will be recorded in the Case Report Form." A discontinuation will be defined: "A discontinuation occurs when an enrolled subject ceases participation in the study, regardless of the circumstances, prior to completion of the protocol." Somewhere in the protocol will be the following sentence: "The final evaluation required by the protocol will be performed at the time of study discontinuation." As in the informed consent document, the protocol does not even suggest a distinction between stopping study medication and stopping the study. A change in definition of discontinuation would emphasize this distinction:

> A discontinuation from study medication occurs when a participant permanently stops taking study medication. A discontinuation from the study occurs when a participant in the study dies, is permanently lost to follow-up, or withdraws consent, regardless of the circumstances, prior to completion of the protocol.

Often protocols have language of the following type:

> Subjects must be withdrawn from the study (i.e., from any further study medication or study procedure) for the following reasons:
>
> - At their own or their legally authorized representative's request.
> - If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.

- Occurrence of an intolerable treatment-emergent adverse event as determined by the investigator and/or the subject.
- Failure of the subject to return to the study site for scheduled visits.
- Persistent noncompliance.
- Pregnancy.

All of these are sensible reasons to stop study medication and many study procedures; only a few are relevant to stopping follow-up.

Table 2 Typical early termination form with items that give little useful information starred

Identify the primary reason the subject has stopped participating in the trial.
☐ Subject died
☐ Subject moved and no longer lives near a participating clinic
☐ Subject experienced an adverse event and no longer wishes to participate
☐ Subject became pregnant
☐ Subject no longer is able to come to the clinic
☐ Lack of efficacy
☐ Subject choice*
☐ Investigator judges further participating is not in the best interest of the subject*
☐ Investigator choice*
☐ Withdrawal of consent*
☐ Other*_____

Along with the preceding list of reasons for withdrawal from the study in the protocol is a related page of the case report form. When a participant no longer wishes to participate in the trial, the investigator fills out an "Early Termination Form" that looks something like Table 2. Note that many of the items in the list are noninformative, and in many trials the noninformative reasons dominate the informative ones.

6. SOME STEPS TO LESSEN MISSING DATA

In order to decrease the amount of missing primary outcome data, our first task as statisticians, individually and collectively, is to educate sponsors and investigators to the pernicious effect of missing data on the inferences drawn from randomized trials. Before the beginning of a trial, we should demonstrate to them the range of results that various methods for dealing with missing data are likely to produce in the context of the particular trial being designed. We need to explain to investigators the importance of complete follow-up, even of those who have stopped taking study medication. We need to review informed consent forms so that participants understand that stopping study medication is not synonymous with stopping the trial. We must be vigilant about permissive language in protocols, paying specific attention to the distinction between stopping study medication and stopping participating in the study completely. Regulatory bodies can play a crucial role in preventing missing data because in the absence of a regulatory requirement—or at least encouragement—to follow all randomized patients, the sponsor who is diligent about follow-up may be at a competitive disadvantage to the sponsor who stops following patients when they discontinue the drug.

When a participant elects to stop study medication, investigators should not automatically assume the participant is withdrawing consent. Some participants will be willing to continue visits; some who are not willing to continue visits will be willing to be followed by telephone or by more passive methods.

If, after all our efforts, some data are missing—and in spite of all reasonable efforts, some missing data are inevitable—the methods we use to deal with missing data should be reasonably conservative, they should not add false precision, and they should be interpretable. They should ask questions like "What would have happened if the patient had been followed off treatment?" and "What would have happened if the patient had switched to standard of care?" The answers to these questions are, of course, conditions contrary to fact. In designing studies, the sample size should account correctly for the expected extent of missing data; inflation by the proportion expected missing is not sufficient to maintain power.

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