

Review

## Problems in dealing with missing data and informative censoring in clinical trials

Weichung Joseph Shih<sup>1,2</sup>

Address: <sup>1</sup>Division of Biometrics, University of Medicine and Dentistry of New Jersey School of Public Health, New Brunswick, New Jersey, USA and <sup>2</sup>Cancer Institute of New Jersey, University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

E-mail: shihwj@umdnj.edu

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### Abstract

A common problem in clinical trials is the missing data that occurs when patients do not complete the study and drop out without further measurements. Missing data cause the usual statistical analysis of complete or all available data to be subject to bias. There are no universally applicable methods for handling missing data. We recommend the following: (1) Report reasons for dropouts and proportions for each treatment group; (2) Conduct sensitivity analyses to encompass different scenarios of assumptions and discuss consistency or discrepancy among them; (3) Pay attention to minimize the chance of dropouts at the design stage and during trial monitoring; (4) Collect post-dropout data on the primary endpoints, if at all possible; and (5) Consider the dropout event itself an important endpoint in studies with many.

### Introduction

With the exception of counting deaths from all causes, a common problem in clinical trials is the missing data caused by patients who do not complete the study in full schedule and drop out of the study without further measurements. Possible reasons for patients dropping out of the study (the so-called 'withdrawals') include death, adverse reactions, unpleasant study procedures, lack of improvement, early recovery, and other factors related or unrelated to trial procedure and treatments. Missing data in a study because of dropouts may cause the usual statistical analysis for complete or available data to be subject to a potential bias. This review attempts to raise the awareness of the problem and to provide some general guidance to clinical trial practitioners.

### Examples

Withdrawals from clinical trials are ubiquitous. The Nuremberg Code, adopted in 1947, established principles of ethical conduct in such trials. These principles demand that the subject be given the choice stop participating at any time during the clinical study. Under these principles, the investigator is obliged to stop the experiment if injury seems likely. I highlight just a few findings from recent articles in the area of cardiovascular medicine for illustration.

#### Example 1:

A multicenter, randomized, double-blind, three parallel groups trial to compare placebo, candesartan ciltixelil and enalapril in patients with mild to moderate essential hypertension [1]. The study randomized 205 to treat-

ment, however, only 178 patients were evaluable by protocol at the end of an 8-week treatment period. 'The remaining patients were excluded from the analysis of blood pressure (BP) data because of major protocol violations, poor compliance with medical visits, or withdrawal because of adverse events.'

**Example 2:**

A multicenter, randomized, open-label, parallel-design study to compare the treatment effect of niacin and atorvastatin (for 12 weeks) on lipoprotein subfractions in patients with atherogenic dyslipidemia [2]. 'Of the total 108 patients randomized to treatment, 12 withdrew from the study. Of those who withdrew, nine were due to adverse events, two were lost to follow-up, and one did not return for the final visit.'

**Example 3:**

A multicenter, randomized, double-blind, placebo-controlled trial to assess treatment effect of pimobendan on exercise capacity in patients with chronic heart failure [3]. 'The primary pre-specified analysis of exercise time was limited to those patients who had at least the first follow up (four-week) exercise test carried out and had shown good compliance up to the day of the test. If subsequent tests were not performed, whatever the reason, or performed although compliance between tests had been poor, the last exercise time value obtained while compliance was good was carried forward.' Two hundred and forty of the 317 randomized patients had exercise test done with good compliance at four, 12, and 24 weeks. Listed reasons (and number of patients) for missing exercise time data at 24 weeks were: 'exercise test not done due to death' (n = 30), 'exercise testing contraindicated' (n = 9), and 'exercise test not done for other reasons' (n = 10).

**Example 4:**

A randomized, double-blind study to compare nifedipine-GITS and verapamil-SR on hemodynamics, left ventricular mass, and coronary vasodilatory in patients with advanced hypertension [4]. Fifty-four patients were randomized after the placebo run-in phase. 'Twenty-four failed to complete the (six-month) trial, and thus were not included for analysis because of 1) withdrawal for symptomatic adverse effects, 2) lack of response, and 3) poor compliance.' 'Consequently, there were 30 subjects with sufficient data sets for inclusion in analyses.'

**Example 5:**

A randomized, double-blind, titration study of omapatrilat with hydrochlorothiazide in comparison with hydrochlorothiazide (HCTZ) plus placebo for the treatment of hypertension [5]. After 2 weeks of placebo lead in and four weeks of HCTZ period, 274 subjects were randomized into three treatment groups. 'A total of 235 sub-

**Table 1: Summary data from Diamond JA et al. [4]**

	Number of Patients (%)
Randomized	54 (100)
Early withdrawal	24 <sup>(d)</sup> (44.4)
Completed 6 months	30 (55.6)
Completed 6 months with controlled BP and no side effects	24 <sup>(cr)</sup> (correct: 24 <sup>(cr)</sup> /54 = 44.4%) (incorrect: 24 <sup>(cr)</sup> /30 = 80%)

jects completed the (eight-week double-blind period) study.'

**Effect of withdrawals on the data analysis**

To demonstrate with simple algebra the effects and key statistical concepts surrounding missing data, I use the data from Example 4 above. In that study, 54 patients were randomized. However, only the 30 patients who completed the trial were included in the paper's analysis. The authors excluded from the analysis the other 24 patients who withdrew early because of adverse effects, lack of response or poor compliance. Defining effective control of BP by the criteria of either maintaining diastolic blood pressure (DBP) ≤ 95 mmHg or achieving a least ≥ 15 mmHg decrease in DBP, the authors summarized the following results: 'Eighty per cent of randomized patients completed the protocol with effective control of BP and no side effects.' Obviously, the authors only counted 24 patients out of the 30 completers and obtained 80% and ignored the 24 patients who dropped out prior to the scheduled end of the study at six months. To distinguish the different 24 patients in this example, we denote 24<sup>(cr)</sup> for the former and 24<sup>(d)</sup> for the latter, that is, dropouts. It is easily seen that the correct summary should be 24<sup>(cr)</sup>/54 = 44.4% completed the protocol with effective control of BP and no side effects, rather than the reported 24<sup>(cr)</sup>/30 = 80%. (See Table 1.)

If the authors really intended to estimate the chance for patients to have effective control of BP with no side effects with the study therapies at Month 6 ('responders' in brief), then we need to do more work. First, the calculation should always use 54 as the denominator because that was the number of patients randomized to the study; however, only 30 patients had BP measurement at Month

**Table 2: Illustration of different methods by example of data from Diamond JA et al. [4]**

	Number of Patients	Responders <sup>+</sup>			
		Observed	Estimated (a) <sup>&amp;</sup>	Estimated (b) <sup>&amp;</sup>	Estimated (c) <sup>&amp;</sup>
Early withdrawal	24 <sup>(d)</sup>	?	0	24	19.2
Completed 6 months	30	24 <sup>(cr)</sup>	24 <sup>(cr)</sup>	24 <sup>(cr)</sup>	24 <sup>(cr)</sup>
Total (%)	54(100)	24 <sup>(cr)+?</sup> (?)	24 (44.4)	48 (88.9)	43.2 (80)

<sup>+</sup>Responder: effective control of BP and no side effects at month 6. <sup>&</sup> (a) and (b) assume two extreme informative missing models, (c) assumes missing completely at random (MCAR) model.

6; of them, 24<sup>(cr)</sup> were responders. This means that the true answer should be  $(24^{(cr)}+?)/(30+24^{(d)}) = (24+?)/54$ , where the question mark represents the unknown number of responders among the 24<sup>(d)</sup> withdrawals counted in the denominator. Next, we calculate the extreme possibilities as (a)  $(24^{(cr)}+0)/54 = 44.4\%$  and (b)  $(24^{(cr)}+24)/54 = 48/54 = 88.9\%$ .

In (a) we assumed that none of 24<sup>(d)</sup> withdrawals (0%) responded, while in (b) we assume all 24<sup>(d)</sup> withdrawals (100%) responded. Of course, we know that (b) is unrealistic since some people withdrew because of lack of response and some because of side effects, but the paper did not provide the exact numbers. In general, we usually do not feel comfortable with either extreme, but we understand that they provide an idea of the uncertainty in the data because of withdrawals.

An estimate between the extremes is (c): to substitute the unknown number by  $24^{(d)} \times (24^{(cr)}/30) = 24^{(d)} \times 0.80 = 19.2$ , where  $24^{(cr)}/30 = 80\%$  is the proportion of responders among those who completed the trial. That is, when no particular information was available, we may assume that the same proportion of patients (80%) among the 24<sup>(d)</sup> dropouts would have also responded, had they completed six months. Unsurprisingly, when we do the calculation, the estimate becomes  $(24^{(cr)}+19.2)/54 = 43.2/54 = 80\%$ , the same answer as that using only the completers. In fact, a simple algebra can show that this is always so. We can see that (c) is in-between (a) and (b), and in this case, leans toward (b). See Table 2.

Notice that the paper reported that a proportion of 80% of 'randomized patients completed the protocol with effective control of BP and no side effects' (as explained earlier, the figure should instead be 44.4%), while the 80% in (c) is an estimate of the chance of effective control of BP without side effects with the study therapies at Month 6,

under an assumption of 'no information available for the missing data'. We should not be confused with these two '80%'. The former 80% is a wrong summary number; the latter is an estimate of the quantity of interest with a particular assumption about the missing data. This assumption is not likely to be appropriate for all the dropouts, especially for those patients who dropped out because of ineffective therapy; more discussion is given later. We do not know whether the authors might have intended to make the latter estimate but gave a wrong summary instead.

Even more interesting and useful would be the same calculations within each treatment group along with a comparison of the estimates. Unfortunately, the paper did not give the number of dropouts according to their treatment groups.

Using proportions simplifies the illustration, but the idea can easily be conveyed to the estimation of continuous data as well, such as BP, exercise time, hemodynamic measures, and lipoprotein levels.

**Lessons learned**

Several points can be generalized from the simple illustration given above and closer examinations of the other examples.

- It does not take very much missing data to mislead an investigator. A good principle to avoid being misled is to always account for every subject randomized to the study in the analysis. Using the total number of randomized subjects in the denominator is a step towards accomplishing this principle, whether it is to calculate an average or a proportion. This principle is known as intent to treat (ITT). However, the much harder job for ITT is to account for the dropouts in the numerator. This requires further consideration, which follows below.

- It is important to record and report the reasons for withdrawal and the number of subjects in each category of withdrawal according to their treatment group. The reasons for patients dropping out can be used to help properly assess the nature of the missing data. For example, if all the dropouts were because of a lack of response or side effects, then the calculation in (a) would be appropriate. In statistical terms, they would be called informative missing data. This is because useful information can be found in the reason for the dropout and this can be used to estimate the true response. Outcome-related dropouts are informative and should not be disregarded in analytical study without careful thought. In particular, when a patient dies, whatever the cause of the death might be, such as in Example 3, all of the subsequent physiological and quality of life data should not even be regarded as missing, but as having values equal to zero or the worst category. When a patient's clinical status has reached a terminal disease progression stage (such as New York Heart Association class IV) and they are unable to perform exercise testing, as in Example 3, the exercise time should also be equal to zero seconds, and not simply regarded as missing data. For the same reason, the remaining survival time after death (of any cause) would be zero days as well, not a censored observation when doing, say Kaplan-Meier, survival analysis for an endpoint such as cardiovascular death. Treating non-cardiovascular death as equivalent to censoring because of loss-to-follow-up or end-of-observation for an endpoint of cardiovascular death has unfortunately become a popular practice in many medical journal articles. This needs to be corrected.

- The extreme calculations in (a) and (b) enable us to assess the uncertainty of the data which contains missing values, especially if we do the calculation for each treatment group separately. The bias seen in the medical publishing industry in the decisions over which articles are chosen for publication is a mirror image of the dropout problem in patient studies. In the former, positive studies have better chance of getting published, while negative studies have a higher chance of being rejected. The same is true for the latter: patients responding to treatment tend to continue in the study, while patients failing to respond tend to drop out prematurely. Using only the available data or only the subgroup of those who complete the study leads to a biased result. The approaches in (a) and (b) take this consideration into account, although they may also be biased by over-correction.

- The assumption underlying the approach in (c) is interesting. When no particular information is known about the missing data, we are essentially assuming that the dropouts are not much different from the completers. This is generally described statistically as missing completely at random (MCAR), meaning that the process which caused

the missing data is not informative about the parameter that we are trying to estimate. A good way to think of MCAR is that the dropouts are a simple, random sample of the study sample. Examples of MCAR include patients who have moved away, or study that has closed and the late entry of patients being administratively 'censored'. We have seen the convenience of MCAR in the above illustration: simply use the completers and we get the same result. However, whether this assumption is valid or not should be examined carefully in each individual case. In many situations, dropouts are not the same patient population as those who stayed within the trial. MCAR certainly is less restrictive than the assumptions in (a) or (b). Still, other less restrictive assumptions than MCAR exist, and these are discussed later.

- All three estimates given by (a), (b), and (c) are biased to a certain extent. Had the authors given the detail about the numbers of dropout categories of 'lack of response' and 'side effects', a better estimate could be derived.

- We would certainly feel more comfortable with a study conclusion when it is not altered by different approaches. Sensitivity analysis is actually the best way to analyze data in the presence of dropouts. Medical investigators should consult with statisticians when dealing with missing data because there are many possible methods available. Some popular approaches are reviewed below.

### More about methods handling missing data

#### Objectives

As in any data analysis, the first consideration is the objective of the analysis. In the presence of dropouts, there can be two types of questions: (i) What would be the treatment effect without dropouts? and (ii) What would be the treatment effect in the presence of dropouts? Question (i) is concerned with an ideal situation. It is also known as a 'question for explanatory trials' [6]. It is often concerned with the human pharmacological properties of new drugs under investigation rather than practical usage. Regarding question (ii), we need to further differentiate two situations: patients drop out either (a) totally from the study and no data are collected after withdrawal, or (b) merely from the study assigned treatment with data still being collected. For (b) there will be no missing data. If we can design trials that will allow patients to be followed until the end of the study despite the patient's lack of compliance, then (ii) is a very practical question, also known as the 'question for pragmatic trials' [7]. Prevention studies with all-cause mortality as the primary endpoint usually follow this design. However, other endpoints may also be followed-up (until death) in such a design. A recent example is [8], in which all participants, even those who discontinued treatment (lovastatin or placebo), were contacted annually for vital status, cardiovascular events,

and cancer history. Since no missing data would occur, the design of (b) is highly recommended for all trials if at all possible. In fact, the ITT principle originally aims to answer question (ii) with (b) type of dropouts, where no missing data would occur. However, more often than not we face studies in which patients have withdrawn from the study entirely and caused the missing data problem, ie, type (a), as the Examples 1–5 (with the exception of Example 3) above have demonstrated. Unless the patient's clinical status does not permit further testing after discontinuing the study treatment, type (a) dropout problem is a common design flaw and should be corrected. Nevertheless, the problem of no follow-up data prevails in clinical trials. For clinical trials conducted for drug registrations it is possible that, in light of the International Conference on Harmonization (ICH)-E9 guideline [9], the data analyses have to address both questions (i) and (ii).

#### **Imputation methods**

The analyses illustrated in Table 2 were methods in the general category of imputation. In general, the basic idea of imputation is to fill in the missing data by using values based on a certain model with assumptions. There are methods based on a single imputation and methods based on multiple imputation, which, instead of filling in a single value for each missing value, replace each missing value with a set of plausible values that represent the uncertainty about the right value to impute. The attraction of imputation is that once the missing data are filled-in (imputed), all the statistical tools available for the complete data may be applied. Each method of (a), (b) and (c) in Table 2 is a single simple imputation method, but together they may be viewed as a 'multiple simple imputation' method (as opposed to the 'proper multiple imputation' method discussed below). The data in Table 2 only had one time-point (Month 6) for analysis.

For longitudinal data with multiple time-points, the conventional last-observation-carried-forward (LOCF) approach is a common practice of another simple imputation. This approach was used by the authors in Examples 3 and 5. Attempting to follow the principle of ITT to account for all randomized, LOCF method includes every randomized subject who has at least one post-therapy observation. LOCF is popular among practitioners because it is simple to put into effect and because of a misconception that it is conservative (meaning working against an effective treatment group). However, every imputation method implicitly or explicitly assumes a model for the missing data. The LOCF assumes (unrealistically) that the missing data after patient's withdrawal are the same as the last value observed for that patient. The consequence of this assumption is that it imputes data without giving them within-subject variability and that it alters the sample size.

Proper multiple imputation (PMI) methods are described in [10] and [11], which use regression models to create more than one imputed data sets and thus provide variability within and between imputations. PMI method has long been a preferred approach in survey research. Its popularity has recently gained in clinical trials since the method became automated by commercial computer software [12,13]. However, the complexity of regression models used in PMI should be carefully thought through by clinical trial practitioners, because the method assumes that the missing data process can be fully captured by the regression model employed on observed values. This assumption is called missing at random (MAR). MAR essentially says that the cause of the missing data may be dependent on observed data (such as data of previous visits) but must be independent of the missing value that would have been observed. It is a less restrictive model than MCAR, which says that the missing data cannot be dependent on either the observed or the missing data. The design suggested by Murray and Findlay [14], which forced dropouts upon observing uncontrolled BP, uses the MAR principle. When MAR or MCAR conditions are met, model-based analyses can be appropriately performed based on the observed data alone without further modeling the missing data process.

Another imputation method, which is in-between the LOCF and PMI, is the partial imputation (PI) or improved LOCF method [15]. The idea of this method is quite simple. In LOCF, one imputes every missing visit time-point by carrying the last observation forward until the end of the study. Since LOCF requires the strong assumption of stability, the more it imputes the more bias it introduces if the assumption of stability does not hold. The method of PI does not always carry the observations to the end time-point of the study, but just far enough to balance the dropout patterns between the treatment groups. The underlying principle is that when the dropout patterns are made almost identical between the treatment groups, the relative comparison of the treatment effects will be less biased. Since PI does less imputation, it is less biased than LOCF because the assumption of stability usually does not hold. Some simulation results under various missing data processes demonstrated the potential usefulness of PI over the methods of using all available data and LOCF [15]. However, more experience is still needed to test this new method in practice.

#### **Methods based on special missing data models**

Other, more sophisticated methods based on statistical models are available [16–18]; a technical review can be found, for example, in [19] and [20]. No general computer programs are available to put them into effect though, because every so-called informative missing data set requires a unique model to describe it.

### Methods based on ranking observations

A large class of non-parametric methods is based on the ranks or 'scores' of the observations instead of the actual values. Commonly used non-parametric methods in clinical trials include the Wilcoxon signed-rank test, Mann-Whitney test, and so on. Example 3 also used a ranking method after LOCF for a secondary analysis. Incorporating missing data into these methods can be easily done, by ranking the missing data, according to the reasons for withdrawals [21], and, in longitudinal study cases, the time of withdrawal [22]. For example, death would be given the worst rank, followed by 'lack of efficacy', then 'adverse reaction', 'patient refusal', and so on. Within the same category of withdrawal, early dropouts would be given worse ranks than later dropouts. Ground rules for the ranking should be set prior to unmasking the treatment codes for data analyses to avoid being post-hoc. After missing data are replaced by their ranks, the usual testing procedure can be carried out. One major drawback in these methods is that they do not provide any estimation of the treatment effect in the original measurement unit, because the data are replaced by the ranks.

All these methods, parametric or non-parametric, require much closer collaboration between medical investigators and statisticians. In the parametric case, the observed outcome cannot provide statistical tests to select the missing data models. In both cases, the validity of the various models or ranking rules requires an examination of the missing data information and strong faith in the reasons given for the patients' withdrawal. Still, the main issue is the question that these methods are addressing. They attempt to follow the ITT principle (but with missing data) to answer question (i) above, hoping that the dropouts can hypothetically be removed by, say, a truly ITT design, or by successfully using concurrent treatments for intolerable side effects without affecting the efficacy of the study medication.

### Composite comparisons

Many believe that removing the patient's dropout process is not plausible in clinical practice. In this case, the dropout process itself may be an outcome of interest and not a nuisance effect. For example, the US Federal Drug Association's draft guidance on diabetes trials specifically requested the consideration of dropouts as an endpoint [23]. Therefore, the problem becomes a 'composite endpoints' issue. This is the approach taken in [24,25], and it has lately been extended to modeling the joint distribution of the longitudinal and time-to-event data (ie, time to withdrawal) [26,27]. In this setting, we would compare the treatment groups with two aspects simultaneously: (a) the chance (or duration) of complying with the prescribed protocol and, (b) the outcome measure (eg, mean change in systolic blood pressure) given the pattern of compli-

ance. The comparison (a) is straightforward by either the standard binomial or survival techniques. The comparison (b) requires the same care as has been discussed here previously, because, given the pattern of compliance, the subgroup of patients has already been self-selected. The randomization mechanism used for achieving comparability between treatment groups is broken by the post-randomization stratification of compliance. It is then important to check the key outcome-correlated baseline characteristics between the treatment groups for any incomparability among these subgroup patients. This was done in Example 4 but not others. Recognizing that the subgroups are no longer randomized, we should treat this portion as a semi-observational study imbedded in the randomized trial. Techniques used for analyzing observational studies should be applied to this part of comparison [28]. Generally speaking, in an observational study, bias can only be reduced but not entirely eliminated by methods of adjustment or matching. Sensitivity analysis in this approach is to consider different baseline covariates for matching or adjustment.

### Conclusion

The issue of what to do about missing data caused by dropouts in clinical trials is a research topic that is still under development in statistical literature. As has been noted in the ICH-E9 guideline [9], 'no universally applicable methods of handling missing values can be recommended.' The issue of handling missing data is intrinsically difficult because it requires a large proportion of missing data to investigate a method. On the other hand, a large proportion of missing data would make a clinical study less credible. The best available advice is to minimize the chance of dropouts at the design stage and during trial monitoring. A truly ITT design is absolutely encouraged. This requires follow-up data to be collected even after patients discontinue the treatment, whenever the clinical status of the patient permits. If it is anticipated that there will be many dropouts, then perhaps the study's duration should be shortened. Alternatively, the medical procedure that is deemed to be the most likely cause of patients' withdrawal should be altered. All data after death of any cause should be given a value of zero instead of a blank. Consideration may also be given to define an endpoint (event), instead of a measurement value, as the primary response variable, which can be determined even if the patient withdraws from the study. In an analysis, one should be clear about the question or objective of the analysis with missing data, and conduct sensitivity analysis with a set of plausible, pre-specified models of the missing data.

### Competing interests

None declared.

## Abbreviations

BP = blood pressure; HCTZ = hydrochlorothiazide; DBP = diastolic blood pressure; ITT = intent to treat; MCAR = missing completely at random; ICH = International Conference on Harmonization; LOCF last-observation-carried-forward; PMI = proper multiple imputation; MAR = missing at random; PI = partial imputation.

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