Advanced Statistics: Missing Data in Clinical Research—Part 1: An Introduction and Conceptual Framework

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Abstract

Missing data are commonly encountered in clinical research. Unfortunately, they are often neglected or not properly handled during analytic procedures, and this may substantially bias the results of the study, reduce study power, and lead to invalid conclusions. In this two-part series, the authors will introduce key concepts regarding missing data in clinical research, provide a conceptual framework for how to approach missing data in this setting, describe typical mechanisms and patterns of censoring of data and their relationships to specific methods of handling incomplete data, and describe in detail several simple and more complex methods of handling such data. In part 1, the authors will describe relatively simple approaches to handling missing data, including complete-case analysis, available-case analysis, and several forms of single imputation, including mean imputation, regression imputation, hot and cold deck imputation, last observation carried forward, and worst case analysis. In part 2, the authors will describe in detail multiple imputation, a more sophisticated and valid method for handling missing data.

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Missing data are ubiquitous in clinical research. It is rare, even under the strictest protocols, to complete a clinical study with absolutely no missing values. While many investigators consider missing data a minor nuisance, ignoring them is potentially very problematic. In fact, investigators should attempt to use all available data to perform the most efficient study possible, to reduce bias, and to provide the most valid estimates of risk and benefit.

Bias, also known as systematic error, is common in clinical research and may result directly from the inappropriate handling of missing values. A primary goal in the analysis of a clinical study is to minimize bias so that valid results are presented and appropriate conclusions are drawn. While bias may be introduced into research through several other mechanisms (e.g., study design, patient sampling, data collection, and or other aspects of data analyses),[1,2] naive methods of handling missing data may substantially bias estimates while reducing their precision and overall study power, any of which may lead to invalid study conclusions.[3] When a large proportion of missing data exists or when there are missing data for multiple variables, these effects may be dramatic. Despite these concerns and the development of sophisticated methods for handling missing data that allow for valid estimates with preservation of study power, many studies continue to ignore the potential influence of missing data, even in the setting of clinical trials.[4–6]

The objectives of this article are 1) to describe typical mechanisms and patterns of missing data in clinical research and their relationships to specific methods of handling missing data, and 2) to describe several simple, yet naive, methods for handling missing data and their limitations. This article will lay the groundwork for a more detailed conceptual framework and practical user guide for the performance of multiple imputation (MI) in the second part of this series.[7]

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CENSORED VALUES AND MISSING VALUES

Throughout both articles, we will make a distinction between censored values and missing values. The term "censored" will refer to the presence of unobserved values in the original data set (Figure 1A). Such a data set will be called "incomplete." Although true values for censored data exist, they are unknown (or censored) to the investigator because they were either not obtained during data collection or not entered during data entry. Conversely, the term "missing" will refer to the actual values that would have been present had they been observed (Figure 1B). While censoring within a data set is known (i.e., either a value is present or not), unless intentionally removed by the investigator, missing values are never known. This terminology is not universal, however, because many investigators use the term "missing" to imply both the pattern of censoring and the unknown values of the censored data. This makes some of the available literature more confusing.

MECHANISMS OF CENSORING OF DATA

To fully understand specific approaches to handling incomplete data, one must be familiar with both mechanisms and patterns of censoring. Although implied, the word "mechanism" in this context does not literally refer to the process by which data became censored. Instead, and somewhat confusingly, it refers to how observed data relate to the pattern of censoring. The appropriate use of specific missing data methods depends strongly on the "mechanism," or more specifically on whether observed values in a given data set are associated with those data that are missing and thus able to "explain" the pattern of censoring.[8,9] Three missing data mechanisms potentially exist, and are referred to as missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).

MCAR

The MCAR mechanism exists when the probability a value is censored is independent of all other observed and unobserved characteristics of the study sample.[8,10] That is, whether a value is censored has no relationship with other known or unknown values in the data set, even if the pattern of censoring (see below) is not random.[3] Thus, for this assumption to exist, subjects with censored data are required to be a random sample of the study population, and those subjects without censored data are required to be a random sample of the source population.[11] This mechanism is the least plausible (i.e., least likely to truly exist) of the three mechanisms, yet it is required for certain missing data methods such as complete-case analysis or available-case analysis (described below) to generate unbiased parameter estimates.

MAR

Assuming a MAR mechanism exists is less restrictive and more tenable than assuming an MCAR mechanism exists and is the principal assumption required for most forms of imputation, including MI.[7] This mechanism requires the pattern of censored values to be completely "explained," or dependent on, observed values in the sample

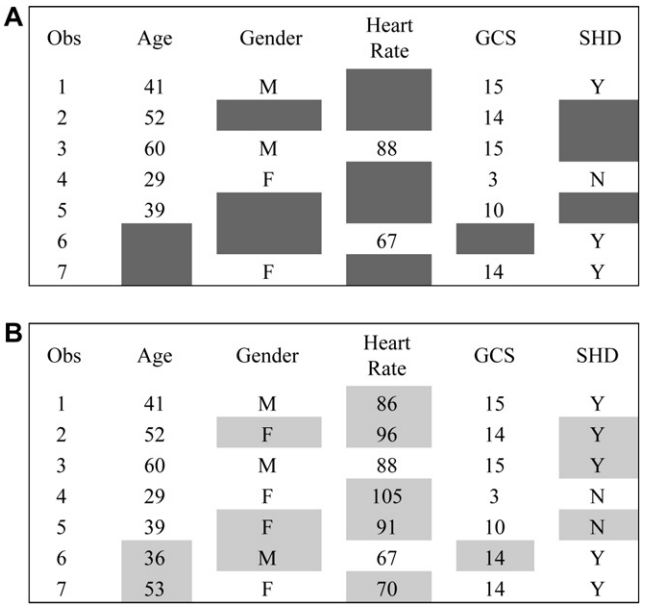

Figure 1. Censored and missing values. Panel A demonstrates censoring, which refers to whether specific values were or were not actually observed in the original data set (dark shaded cells indicate censored values). Panel B demonstrates missing values, which refers specifically to those values that would have been present had they been observed (light shaded cells indicate those cells with missing values as they relate to censored data in Panel A). Abbreviations: Obs = observation; GCS = Glasgow Coma Scale score; SHD = survival to hospital discharge.

but not dependent on any unobserved or missing values.[8,11,12] In other words, in a given data set (Y) consisting of observed values (Y_{obs}) and missing values (Y_{mis}), MAR is present if the probability that a value is censored is dependent only on Y_{obs} and not on Y_{mis}.[8,13] Additionally, whether values are censored may be related to other variables of interest (including those not present in the data set), but these relationships must be fully "explained" by observed values in the data set.[3,8] Although somewhat confusing, this mechanism is referred to as MAR because, conditional on observed characteristics of the sample, the data are missing at random.[11] This mechanism is also often referred to as "ignorable" because observed values are used to estimate the missing values for those that are censored, and thus the pattern of censoring can be "ignored."[3,8,12]

While certain naive methods for handling incomplete data (e.g., complete-case analysis, available-case analysis, and the missing indicator method) are likely to generate biased results under a MAR mechanism, because the data would have to be MCAR for these methods to work, the MAR assumption is necessary and sufficient to justify handling missing data using more sophisticated techniques (e.g., MI or maximum likelihood estimation) to produce valid estimates.[8] Unfortunately, the MAR assumption cannot be tested and must be assumed unless censoring is explicitly introduced into the design of the study.[8,10,14]

MNAR

The MNAR mechanism is present when the pattern of censoring is related to variables that were not collected

and are not related to Y_{obs}, or to Y_{mis} rather than to Y_{obs}.[11] As such, it is impossible to estimate the missing values that are censored from other known values in the data set.[8] This underlying mechanism of censoring is often referred to as "nonignorable" because the probability that a value is censored depends on other unknown or missing values.[12,13] To identify MNAR as the existing mechanism, data must be available to fully explain the pattern of censoring.[11] Unfortunately, this never occurs when censoring is beyond the investigator's control and rarely occurs otherwise. Available methods of handling incomplete data with an MNAR mechanism may not produce valid results, and there is no universal method for handling incomplete data in this situation.[11] However, some methods (e.g., MI) have been shown to produce less biased results than other methods, even when data are MNAR.[10]

One cannot routinely distinguish between the three mechanisms of censoring, and thus in practice, incomplete data are typically assumed to conform to the MAR mechanism even if they may not. Incomplete data rarely conform to the MCAR mechanism and, although one cannot routinely distinguish between MAR and MNAR, an MNAR mechanism can approach an MAR mechanism when additional variables are collected that are associated with the pattern of censoring.[10] Inclusion of strong predictor variables, or variables associated with the pattern of censoring of key variables, may make the MAR assumption much more plausible.[10] While MAR-based approaches are used because they are considered most practical, it is important to recognize that the results of the analyses may depend strongly on the assumed mechanism and, similar to assumptions required by other forms of statistical analyses (e.g., the binomial distribution and its relationship to logistic regression analysis), if they are not met, the results are likely to be invalid.

PATTERNS OF MISSING DATA

The underlying pattern of censoring of data is also important when selecting a method for handling incomplete data (Figure 2). Certain methods for handling incomplete data are generally recommended when specific patterns of censoring are present, while other methods are more versatile. For example, in survey research, it is common to have two forms of censored data, namely, unit nonresponse (where the entire data collection procedure failed because the subject refused or was not available to participate) or item nonresponse (where partial data are available because the subject chose to answer selected individual questions). In this specific situation, it is more reasonable to use weighting techniques for unit nonresponses and imputation for item nonresponses.[12,14]

Although multiple patterns of censoring have been described, the most commonly noted patterns, and those most important for selection of a missing data methodology, are categorized into monotone and nonmonotone patterns (Figure 2B and C). A monotone pattern is present when the incomplete data can be arranged into rows (observations) and columns (variables), resulting in a sequential order of censored values by variable.[8,12] That is, the data can be arranged so each successive variable has fewer observed values (i.e., more censored values) than its predecessor.[8,12] One example of such a pattern can be seen with attrition in longitudinal studies, where time-dependent measures obtained in successive follow-up periods are sequentially censored in subjects who did not complete follow-up.[15,16] In this case, the subjects would be listed in the order of less and less follow-up. Due to its relationship to longitudinal research, this pattern is not common in most clinical studies. However, there are several approaches to handling missing data

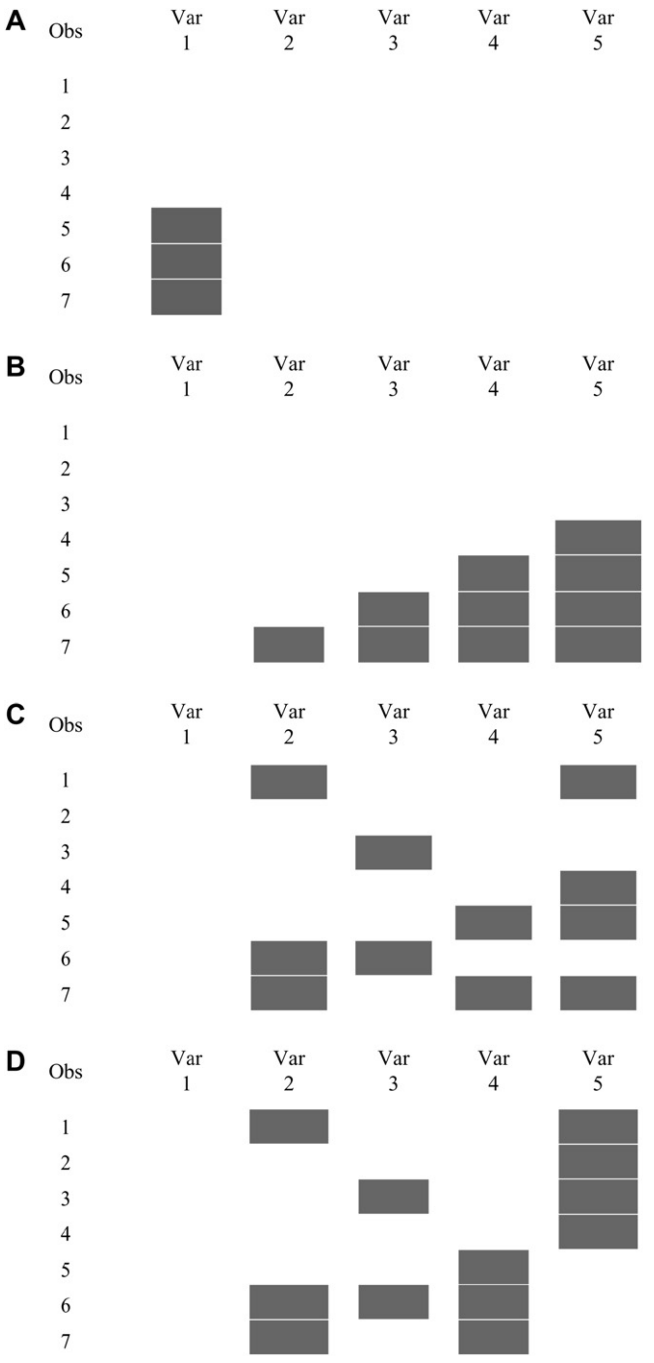

Figure 2. Common patterns of censored data. Shaded cells represent censored data. (A) Univariate, (B) monotone, (C) nonmonotone (general), and (D) two variables never jointly observed (variables 4 and 5). Obs = observation; Var = variable.

when a monotone pattern exists that will not be discussed in this series.[15]

A much more common pattern of censoring appears relatively arbitrary and is referred to as a nonmonotone pattern. All of the methods for handling incomplete data described in this and the companion article will focus on techniques applied to this pattern of censoring (Figure 2C).[8] Nonmonotone data cannot be sorted into a sequential order of censoring and represent a more realistic, almost haphazard pattern that is quite common in clinical research. Within this general pattern of censoring, there may be univariate nonresponse (censored values confined to a single variable) (Figure 2A) or multivariate nonresponse (censored values present in multiple variables) (Figure 2C).[8]

The final general pattern of censoring exists when two variables are never jointly observed.[8] As demonstrated in Figure 2D, there is perfect separation between observed (or censored) values for variables 4 and 5. This pattern may be seen when large amounts of data are censored for multiple variables, and it is important to recognize because it may eliminate important relationships between variables and suggests that parameters dependent on the relationship between such variables are not measurable.[8] Such a pattern requires the assumption that there is no association between the variables that are not jointly observed; if this assumption is not true, the subsequent results may be misleading.

METHODS FOR HANDLING INCOMPLETE DATA

Many methods have been developed and used to perform analyses of partially censored data. In the remaining sections of this article, we will describe several of the more commonly described but relatively naive methods, including 1) procedures based on completely recorded units (i.e., complete-case analysis and available-case analysis), 2) weighted procedures, and 3) single imputation-based procedures.[8,12,17] Although these techniques vary with respect to their levels of sophistication, they are generally considered more simple, more biasing, and less predictable than more sophisticated missing data techniques like MI. Therefore, such methods are generally not recommended when a reasonable proportion of data are censored.

Complete-case Analysis

Complete-case analysis (also known as casewise deletion or listwise deletion) excludes observations with censored values for the variable or variables of interest, thus limiting the analysis to those observations for which all values are observed.[8,12,18] This approach has been widely used and is still an extremely common method of handling data sets with censored values, particularly because of its simplicity. It is frequently the default method for handling incomplete data by statisticians and many statistical software programs. Unfortunately, this method has substantial and important disadvantages. Complete-case analysis results in loss of precision of reported estimates because of the reduction in the sample size and will likely bias the estimates, unpredictably, unless censored values are MCAR and thus the complete cases are a random sample of all cases (see Figures 2–5 in the article by Newgard and Haukoos in this issue of *Academic Emergency Medicine*[7]).[8,13,14,18–23] This method is only justifiable when the loss of precision and potential for bias are believed to be minimal, usually when the proportion of complete cases is high, although a small proportion (i.e., <5%) of censored data may still bias estimates substantially.[8] Unfortunately, the degree of bias and reduction in precision can be difficult to predict using complete-case analysis, because they depend not only on the proportion of censored data but also on the underlying pattern of censoring, the extent to which complete cases differ from incomplete cases, and the parameters of interest.[8] In multivariable models, regression coefficients will be biased if the probability of being a complete case (i.e., those cases with no censored values) depends on the modeled outcome after controlling for the effects of other covariates.[17,18]

Available-case Analysis

Available-case analysis (also known as pairwise deletion) is a form of complete-case analysis that limits analyses to cases with observed values for single variables that are being described or compared statistically.[8,14] Available-case analysis is applied most commonly in situations where complete-case analysis would exclude patients who otherwise have data for calculations of descriptive statistics for individual variables (i.e., univariate statistics) or comparisons between two variables (i.e., bivariate testing). While this technique may be more efficient than complete-case analysis, the principal disadvantages of this method include variation in the number of cases available for different analyses, reduction in precision of estimates that may differ based on the different variables being compared, and the potential for bias as described for complete-case analyses.

Weighted Complete-case Analysis

Weighted complete-case analysis is a modification of complete-case analysis that differentially weights complete cases and incomplete cases to adjust for potential bias.[8] Weighting methods are often used in studies involving survey data, where unit nonresponse is weighted differently in the analysis.[12,14] Weighting observed versus unobserved cases allows for adjustment for potential bias introduced by subjects who fail to respond but who otherwise would be eligible for inclusion in the study.[24,25] Although weighting may reduce bias in subsequent results, the variance is increased using such methodology, thus reducing the precision of estimates.[25] Appropriate calculation of variance in such an analysis can be complicated, and weighting is best used for larger data sets where the potential for bias is more concerning than loss of precision.[25]

Single Imputation

Imputation refers to replacing censored values with values that are, in theory, approximate to the missing values (i.e., values that would have been observed had they not been censored).[8,10,13,14,17,18,21] Single imputation refers to imputing one plausible value for each censored value for a particular variable within a data set and then conducting the analyses as if all data were originally observed. This is a relatively basic approach to handling

missing data that fails to account for the uncertainty inherent in imputing censored values. This failure results in inappropriately small variances and thus apparent precision that is too great (see Figure 4 in Newgard and Haukoos[7]).[8,12,26] Several forms of single imputation are described below.

Mean and Median Imputation. The most basic forms of single imputation are mean or median imputation. These techniques replace censored values with the mean or median values for the same variable, calculated from observed data.[8] Although this relatively popular approach allows for the inclusion of all observations, it can lead to biased parameter estimates (unless the data are MCAR) because censored values are replaced with values at the center of the distribution for that particular variable.[8,10,27] Regardless of the censoring mechanism, the variance will be underestimated and will become progressively, and inappropriately, smaller as the proportion of censored values increases, thus artificially and inappropriately improving the apparent precision of estimates and increasing the probability of a type I error (see Figure 4 in Newgard and Haukoos[7]).[10,16] Attempts to adjust for the artifactually smaller variance have been reported, although they are not typically recommended because they rely solely on available data.[8] An extension of this form of single imputation (called conditional mean or median imputation) uses weighted adjustments, analogous to the weighting described above, to more accurately impute the missing values for censored data when stratified by observed data.[8]

Regression Imputation. Regression imputation involves conducting a regression analysis using observed data and then replacing censored values by single predicted values from the regression analysis. Although this method may generate reasonable approximations for missing values (depending on the mechanism of missingness), the approach underestimates the variance because no additional variance is included with the imputation.[8,10] As this relates to the discussion of MI in the second article of this series, the between-imputation variance is assumed to be zero because only one value exists.[7]

Stochastic Regression Imputation. Stochastic regression imputation provides an additional level of sophistication to regression imputation by replacing censored values with the predicted value from a regression analysis plus its residual error.[10] This approach incorporates uncertainty into the predicted value and thus accounts for some additional variance in the imputed estimates, thus improving upon the primary limitation of precision for simple regression imputation. The estimates resulting from both regression imputation techniques will depend heavily on how the data are modeled. Semiparametric and nonparametric forms of regression, as well as other forms of multivariable regression modeling, have been used to impute censored values, although they still generally fail to fully account for the uncertainty (i.e., additional variance) inherent in the imputation process.[16,17]

Hot and Cold Deck Imputation. Hot deck imputation is a method of imputing values identified from "similar" available cases within the same data set. In general, each censored value is replaced by an observed value from a case that is similar to the case with the censored value.[10,12] Although many variations and modifications of this method exist,[8] one common approach uses simple random sampling with replacement from all complete cases identified as being similar to the case with the censored value and replaces the censored value with the observed value for the same variable in the similar case sampled. This process continues until all censored values for the variable or variables of interest have been replaced.[28] This technique generally underestimates the variance of the parameter estimate because the variation introduced into the imputed analysis is only consistent with the ranges from complete cases identified as being similar to those with missing data.[28] Variance is also underestimated because only a single specific value is imputed for each censored value. The principal advantages of this technique are that it does not require parametric assumptions or careful modeling to identify values to impute and that variation of imputed values may better reflect the distributional properties of the variable.[10,29] Disadvantages of this technique include the potential for bias because imputed data result solely from complete cases, the need to potentially adjust for variance as mentioned with previous techniques, the need for an adequate number of complete cases to match against (i.e., large sample size with little or modest amounts of missing data), and that there are no clear criteria to guide selection of complete cases to match against cases with missing data.[28] It is this last selection process that is used to address the MAR assumption.

Cold deck imputation replaces censored values with values from an external data source using similar methodology as that described for hot deck imputation. This form of imputation, however, has additional disadvantages when compared with hot deck imputation. Specifically, data from the external source may differ systematically from those of the primary data set, thus adding an additional level of bias to the parameter estimates.[8,30] This technique has not been widely adopted and is also generally not recommended.

Last Observation Carried Forward. Last observation carried forward is another form of single imputation used primarily for analyses of longitudinal studies that have experienced attrition.[14] This approach uses all subjects and imputes the censored values with the last observed value for that subject, using the primary, and likely incorrect, assumption that the value did not change from the previous value. An extension of this technique uses linear interpolation from two adjacent observations or linear extrapolation from two prior observations to impute missing values, assuming the trajectory between or after the two data points is linear.[13] These methods of imputation will obviously introduce bias if these assumptions are not met.[31]

Last observation carried forward has been traditionally recommended by the Food and Drug Administration in an effort to report "more conservative" estimates than when using only observed cases.[32,33] Recognizing the limitations of this approach, the Food and Drug Administration has more recently begun to recommend more sophisticated incomplete data methods such as MI.[34]

Worst Case Analysis. Worst case analysis is an approach commonly used when outcome data are censored, although it can be used when predictor data are censored as well.[6,35] This method imputes worst case values (e.g., imputing death for a binary survival outcome variable for all experimental treatment subjects with a censored outcome) for those data that are missing in an effort to define the range of possible results under a "worst case scenario."[36] This technique is not intended to result in a likely valid data set, but instead to demonstrate that censoring could not have qualitatively affected the study outcome, when this is indeed the case.

Missing Indicator Method. Using a missing indicator variable is another relatively simple approach for handling censored data when using a regression analysis.[17] For each variable (X_i), a "missing value" indicator variable (M_i) is created that takes the value of "1" when the original variable is censored and "0" when the original variable is present. The original variable (X_i) is then replaced in the regression model with the missing indicator plus the product of the original variable and the missing value indicator $[M_i + X_i(1 - M_i)]$. When the value is present in the data set (i.e., $M_i = 0$), this latter expression reduces to X_i the original variable. When the value is censored in the data set (i.e., $M_i = 1$), this expression reduces to "1." This allows for all observations to be included in the analysis while controlling for whether values are censored.[17,37] Unfortunately, this technique introduces bias and creates invalid variance estimates under most circumstances, the magnitude of which will depend heavily on the nature of the variable (i.e., whether it is continuous, and if so, the range of values for the variable, or categorical, and if so, the number of categories and how they are categorized).[18] It is therefore not recommended except in unusual circumstances.

CONCLUSIONS

Incomplete data are a pervasive problem in clinical research, and ignoring them or handling them inappropriately may bias study results, reduce power and efficiency, and alter important risk/benefit relationships. Appropriate handling of censored values in clinical research should be a substantial concern of investigators, and planning for the integration of valid incomplete data methods into the analysis is important. Unfortunately, the use of simple techniques often results in biased and potentially misleading conclusions.

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References

1. Schriger DL. Suggestions for improving the reporting of clinical research: the role of narrative. Ann Emerg Med. 2005; 45:437–43.
2. Rothman KJ, Greenland S. Modern Epidemiology, 2nd ed. Philadelphia: Lippincott-Raven, 1998.
3. Collins LM, Schafer JL, Kam CM. A comparison of inclusive and restrictive strategies in modern missing data procedures. Psychol Methods. 2001; 6:330–51.
4. Little RJ. Methods for handling missing values in clinical trials. J Rheumatol. 1999; 26:1654–6.
5. Auleley GR, Giraudeau B, Baron G, et al. The methods for handling missing data in clinical trials influence sample size requirements. J Clin Epidemiol. 2004; 57:447–53.
6. Wood AM, White IR, Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. Clin Trials. 2004; 1:368–76.
7. Newgard CD, Haukoos JS. Advanced statistics: missing data in clinical research—part 2: multiple imputation. Acad Emerg Med. 2007; 14:669–78.
8. Little RJA, Rubin DB. Statistical Analysis with Missing Data, 2nd ed. Princeton, NJ: Wiley, 2002.
9. Rubin DB. Inference and missing data. Biometrika. 1976; 63:581–92.
10. Sinharay S, Stern HS, Russell D. The use of multiple imputation for the analysis of missing data. Psychol Methods. 2001; 6:317–29.
11. Donders ART, Van der Heijden GJMG, Stijnen T, et al. A gentle introduction to imputation of missing values. J Clin Epidemiol. 2006; 59:1087–91.
12. Rubin DB. Multiple Imputation for Nonresponse in Surveys. NY: Wiley, 1987.
13. Shafer JL. Multiple imputation: a primer. Stat Methods Med Res. 1999; 8:3–15.
14. Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods. 2002; 7:147–77.
15. Twisk J, de Vente W. Attrition in longitudinal studies: how to deal with missing data. J Clin Epidemiol. 2002; 55:329–37.
16. Magnusson D, Bergman LR. Data Quality in Longitudinal Research. NY: Cambridge University Press, 1990.
17. Schafer JL. Analysis of Incomplete Multivariate Data. Boca Raton, FL: Chapman & Hall, 1997.
18. Greenland S, Finkle WD. A critical look at methods for handling missing covariates in epidemiologic regression analyses. Am J Epidemiol. 1995; 142: 1255–64.
19. Vach W, Blettner M. Biased estimation of the odds ratio in case-control studies due to the use of ad hoc methods of correcting for missing values for confounding variables. Am J Epidemiol. 1991; 134: 895–907.
20. Joseph L, Belisle P, Tamim H, et al. Selection bias found in interpreting analyses with missing data for the prehospital index for trauma. J Clin Epidemiol. 2004; 57:147–53.
21. Hawthorne G, Elliott P. Imputing cross-sectional missing data: comparison of common techniques. Aust N Z J Psychiatry. 2005; 39:583–90.
22. Beunckens C, Molenberghs G, Kenward MG. Direct likelihood analysis versus simple forms of imputation for missing data in randomized clinical trials. Clin Trials. 2005; 2:379–86.
23. Moore L, Lavoie A, LeSage N, et al. Multiple imputation of the Glasgow Coma Score. J Trauma. 2005; 59: 698–704.

24. Little RJ, Vartivarian S. On weighting the rates in non-response weights. Stat Med. 2003; 22:1589–99.
25. Little RJ, Lewitzky S, Heeringa S, et al. Assessment of weighting methodology for the National Comorbidity Survey. Am J Epidemiol. 1997; 146:439–49.
26. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991; 10:585–98.
27. Crawford SL, Tennstedt SL, McKinlay JB. A comparison of analytic methods for non-random missingness of outcome data. J Clin Epidemiol. 1995; 48:209–19.
28. Perez A, Dennis RJ, Gil JFA, et al. Use of the mean, hot deck and multiple imputation techniques to predict outcome in intensive care unit patients in Columbia. Stat Med. 2002; 21:3885–96.
29. Cochran WG. Sampling Techniques. NY: Wiley, 1977.
30. Holman R, Glas CA, Lindeboom R, et al. Practical methods for dealing with "not applicable" item responses in the AMC Linear Disability Score project. Health Qual Life Outcomes. 2004; 16:29. Available at: http://www.hqlo.com/content/pdf/1477-7525-2-29.pdf. Accessed May 10, 2006.
31. Houck PR, Mazumdar S, Koru-Sengul T, et al. Estimating treatment effects from longitudinal clinical trial data with missing values: comparative analyses using different methods. Psychiatr Res. 2004; 129:209–15.
32. Lesaffre E, Verbeke G. Clinical trials and intervention studies. In: Everitt BS, Howell DC, eds. Encyclopedia of Statistics in Behavioral Sciences. NY: Wiley, 2005.
33. Mathews M, Adetunji B, Mathews J, et al. Child psychopharmacology, effect sizes, and the big bang [letter]. Am J Psychiatry. 2005; 162:818.
34. U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Population Pharmacokinetics. Available at: http://www.fda.gov/cder/guidance/1852fnl.pdf. Accessed Sep 18, 2006.
35. Unnebrink K, Windeler J. Sensitivity analysis by worst and best case assessment: is it really sensitive? Drug Inf J. 1999; 33:835–9.
36. Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. J Clin Epidemiol. 2005; 58:579–88.
37. Li X, Song X, Gray RH. Comparison of the missing-indicator method and conditional logistic regression in 1:m matched case-control studies with missing exposure values. Am J Epidemiol. 2004; 159:603–10.