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Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals

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Background Randomized controlled trials almost always have some individuals with missing outcomes. Inadequate handling of these missing data in the analysis can cause substantial bias in the treatment effect estimates. We examine how missing outcome data are handled in randomized controlled trials in order to assess whether adequate steps have been taken to reduce nonresponse bias and to identify ways to improve procedures for missing data.

Methods We reviewed all randomized trials published between July and December 2001 in *BMJ, JAMA, Lancet* and *New England Journal of Medicine*, excluding trials in which the primary outcome was described as a time-to-event. We focused on trial designs, how missing outcome data were described and the statistical methods used to deal with the missing outcome data, including sensitivity analyses.

Results We identified 71 trials of which 63 (89%) reported having partly missing outcome data: 13 trials had more than 20% of patients with missing outcomes. In 26 trials that measured the outcome at a single time point, 92% performed a complete case analysis and 8% imputed the missing outcomes using baseline values or the worst case value. In 37 trials with repeated measures of the outcome, 46% performed complete case analyses, potentially excluding individuals with some follow-up data, while 14% performed a repeated measures analysis, 19% used the last observation carried forward, 11% imputed with the worst case value and 2% imputed using regression predictions. Thirteen (21%) of trials with missing data reported a sensitivity analysis.

Conclusions Our review shows that missing outcome data are a common problem in randomized controlled trials, and are often inadequately handled in the statistical analysis in the top tier medical journals. Authors should explicitly state the assumptions underlying the handling of the missing outcomes and justify them through data descriptions and sensitivity analyses. *Clinical Trials* 2004; **1**: 368–376. www.SCTjournal.com

Introduction

Randomized controlled trials are the cornerstone of evidence-based medicine because they have the potential to produce unbiased estimates of treatment effects. This potential may be compromised when individuals in the trial have missing outcome data since inadequate handling of the missing data can lead to substantial bias in the results. In particular, the intention to treat strategy, designed to compare all randomized individuals irrespective of missing outcomes or treatment changes, cannot be directly adopted when there are missing outcome data [1]. Missing baseline data usually do not lead to bias but can reduce precision [2].

To draw inferences in the presence of missing outcome data it is almost always necessary to make some assumptions. Many methods make assumptions about how the probability of an outcome being missing relates to baseline covariates and

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outcomes. Little defines the following situations [3]. Data are "missing completely at random" (MCAR) if the probability of a missing outcome is the same for all individuals in the trial, and hence does not depend on baseline covariates or outcomes. More general is "covariate-dependent missing completely at random" (CD-MCAR), where missingness can depend on baseline covariates but not on any outcomes. A simple complete case analysis, which restricts attention to individuals for whom the outcome of interest is observed, is valid under the MCAR assumption, and possibly under CD-MCAR if adjustment is made for appropriate baseline covariates. Often CD-MCAR is not distinguished from MCAR and, for the purpose of this paper, we will class them together as MCAR.

"Missing at random" (MAR) further allows missingness to depend on any observed data, including observed postbaseline outcomes. For example, missingness might be determined by the observed outcome of the patient as the trial progresses [4]. A likelihood-based analysis using only the observed data can be valid under the MAR assumptions, with a correctly specified model. Finally, "missing not at random" (MNAR) is used to describe situations where the probability of a missing outcome depends on unobserved outcomes, as well as on the observed data. This arises, for example, when individuals leave a study because of a deterioration or improvement in their condition. Parameter estimation from the observed data alone is typically biased, to an extent that depends on the proportion of dropout and the strength of the relationship between the unobserved outcome and probability of dropout.

Some common procedures make assumptions that do not fall under the hierarchy above. A crude, yet popular imputation technique is last observation carried forward (LOCF) [5], which makes use of baseline measurements and any observed intermediate measurements by carrying forward the last observation to the final time point for patients who drop out. LOCF makes the assumption that an individual's missing value has not changed from the previously measured or baseline value for that individual and that there is no uncertainty in this estimate. An alternative approach is to impute with the worst case value, if such a value exists, although this rarely leads to unbiased results for the treatment effects [6]. The assumption is that dropout implies poor outcome. In any analysis, it is important that the assumptions made should be clearly stated, justified and checked as far as possible. In the presence of missing data, sensitivity analyses should explore the robustness of conclusions to alternative plausible assumptions.

There is a large literature comparing methods to handle missing outcomes [7–10] and developing complex statistical procedures for handling MNAR situations and performing sensitivity analyses

Table 1 Summary of possible analyses when there are missing outcome data

Analysis	Description of method	Assumptions	Adequacy for addressing missing data
Complete case	Excludes subjects with missing outcome	The excluded group are a random sample of all randomized subjects	Only valid under missing completely at random. Loss of power with repeated measures
Last observation carried forward (LOCF)	Imputes missing values with the individual's last observation	The missing value is exactly the same as previous measurement	Rarely believable: can be conservative but hard to know if this is so
Worst case imputation	Imputes all missing values with the worst case value	Individuals with missing values are worse (poor health) than observed individuals	Ad-hoc and too extreme; rarely leads to unbiased results
Regression imputation	Missing outcomes are predicted from the individuals' observed data, using a model based on observed individuals	Missing outcomes can be explained by the individuals' observed data	Can be valid under missing at random. Single imputation under-estimates standard errors, but multiple imputations corrects this
Repeated measures	All observed outcomes are modelled, allowing for correlation between the individual's observations	Missing outcomes can be explained by the individuals' observed data	Repeated measures ANOVA can be valid under missing at random, and GEEs are valid under missing completely at random
Sensitivity analysis	Analyses which directly assess the assumptions made in primary analysis	Can be used to address the missing not at random assumption.	Essential to assess the robustness of the analyses and conclusions; should be used to address potential bias

[11–15]. The aim of this study is to investigate the methods currently adopted in the medical literature and to raise awareness of common problems and their solutions.

Methods

We hand-searched the *British Medical Journal, Journal of the American Medical Association, The Lancet* and *New England Journal of Medicine* for reports of single randomized trials published between July and December 2001. Additional tables and results from journal websites were checked if referred to in the article. We excluded any trials in which the outcome of primary interest was a time to some event, since these raise different issues [16]. We excluded two further trials in which the proportion of individuals with missing data was the primary outcome.

For each trial we recorded the proportion of individuals with missing primary outcome, and the method used to handle the missing data in the principal analysis. When several primary outcomes were reported we used the first one listed. When the primary outcome variable was observed repeatedly over time, we used the final observation as the primary outcome unless the paper defined it as at an earlier follow-up time. We defined the principal analysis as the major analysis presented of the primary outcome. We identified the statistical methods used in the primary analysis (Table 1) and whether all randomized individuals were analyzed or whether exclusion criteria were enforced. This was determined either from the text or from denominators in tables and figures. Sensitivity analyses were defined as any analyses of the primary outcome other than the principal analysis, especially those used to check the robustness of conclusions to different approaches to handling the missing data. Adjustment for baseline variables was not regarded as a sensitivity analysis.

Initial assessments of all trials were carried out by one assessor (AW) and a random selection of 20% was appraised independently by a second assessor. Kappa statistics measuring interrater agreement [17] between the number of missing outcomes, methods used to deal with missing data and whether a sensitivity analysis was performed were 0.86, 1.00 and 0.63, respectively. All discrepancies were resolved by discussion between assessors.

Results

We identified 71 randomized trials meeting our inclusion criteria from the four journals; Table 2 summarizes their characteristics. All trials except one reported the number or proportion of subjects with missing primary outcomes; in the one exception it was clear that there were missing data. Figure 1 displays the proportions of randomized patients with missing outcomes. Sixty-three trials (89%) had some patients with missing primary outcomes. Twenty-six of these 63 trials measured the outcomes at a single time-point while the other 37 trials collected repeated measures of the outcome. The median percentage of missing outcomes was 10%, and 13 (18%) trials had more than 20% missing outcomes.

Table 2 Description of trials included in the study

Characteristic		No. of trials ($n = 71$)
Journals	*BMJ*	18 (25%)
	JAMA	15 (21%)
	Lancet	18 (25%)
	NEJM	20 (28%)
Subjects per trial	Median (IQR)	320 (116–771)
Number of centres involved	Single centre trial	25 (35%)
	Multi centre trial	46 (65%)
Method of collecting primary outcome	Hospital/clinic visits	46 (65%)
	Home visit/post/telephone	18 (25%)
	Other	7 (10%)
Type of primary outcome	Binary	22 (31%)
	Categorical	13 (36%)
	Quantitative	36 (51%)
Number of outcome measurements	Single	34 (48%)
	Repeated	37 (52%)

Figures are numbers of trials and percentages in brackets, unless otherwise indicated.

Of the 63 reports of trials with missing outcome data, 46 (73%) presented a sample size calculation and 20 (32%) accounted for missing outcome data in the calculation. Attempts to avoid missing data before and during the trial were mentioned in 18 (29%) studies. Most commonly, telephone calls were made to reschedule visits or patients were contacted at home.

Description of missing data

Fifty-six trials reported the number of patients with missing outcomes by randomized treatment arm (89% of trials with missing outcome data). Twelve (19%) trials further reported a significance test between the proportions missing by treatment arm and five had significant differences. Thirty-eight (60%) trials with missing data reported reasons why the outcomes were missing. Comparisons of baseline characteristics between patients with observed and missing outcomes were reported in 17 (27%) trials, five of which reported significant differences. Twenty-six (41%) trials presented comparisons of

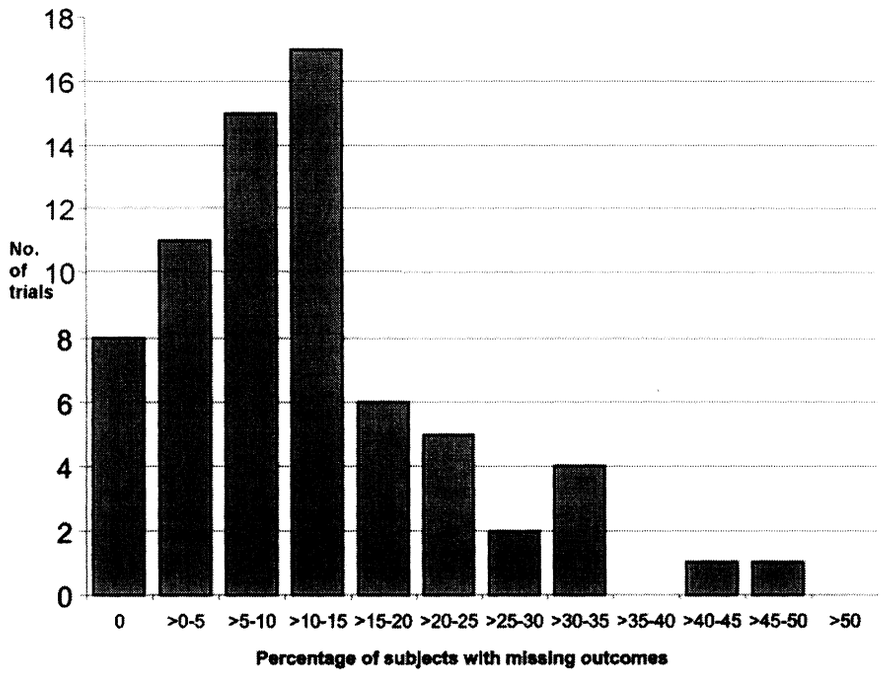

Figure 1 The distribution of the percentage of subjects with missing outcome data from 70 trials under study: one trial is excluded which did not give the percentage of missing data.

baseline characteristics between treatment arms for patients with observed outcomes. Five of these reported significant differences.

Handling of missing data in primary analysis

Amongst the 63 trials with missing data, 41 (65%) trials used complete case analysis in the primary analysis (Tables 3 and 4); 17 of these trials collected repeated measures and so potentially excluded patients for whom some intermediate measurements were available. Complete case analyses were not restricted to trials with smaller percentages of missing data. In total, 15 (24%) trials imputed values for the missing outcomes (Tables 3 and 4): seven trials used the LOCF, five trials imputed with the worst case value, one trial used the nearest measurement in time (either previous or future measurement), one trial imputed with regression predictions obtained from the observed data and one trial performed multiple imputations. Five (8%) trials used repeated measures analyses that were able to include patients with incomplete follow-up. Imputation and repeated measures techniques enabled 10 (16%) trials to include all randomized patients in the analysis and 10 (16%) trials to include some patients who had intermediate measurements but not the final outcome (Table 4). Over all 63 studies, the median percentage of patients who were excluded from the primary analysis was 9% [interquartile range (IQR) 1–15%].

In total, 26 (41%) trials explicitly stated that the analysis was "intention to treat" but only seven of these trials included all patients.

Table 3 The statistical methods used to handle missing outcomes in 26 published trials which measured the outcome at a single time point, according to which patients were included in the primary analysis and the proportion of missing outcome data

Method used in primary analysis	<10% missing outcome data	≥10% missing outcome data
Complete case	10	14
Impute all missing values with:		
Baseline carried forward	1	0
Worst case	1	0

Sensitivity analysis

Thirteen (21%) trials with missing data reported a sensitivity analysis in an attempt to relax the assumptions made about the missing data (Table 5). Levels of reporting the sensitivity analysis varied, from a single sentence saying one was performed, to tabulation of the results. The sensitivity analyses were performed on trials with relatively high

Table 4 The statistical methods used to handle missing outcomes in 34 published trials with repeated measures data, according to which patients were included in the primary analysis and the proportion of missing outcome data

Method used in primary analysis	Inclusion criteria[a]	<10% missing outcome data	≥10% missing outcome data
Complete case	final outcome	7	10
Impute missing values with:			
Last observation carried forward	all	1	1
	any outcome	0	3
Worst case	all	1	2
	any outcome	0	1[b]
Nearest value	all	0	0
	any outcome	1	0
Regression imputation	all	1	0
	any outcome	0	0
Multiple imputation	all	0	0
	any outcome	0	1
Model repeated measures:			
Generalizing estimating equations (GEEs)	all	0	0
	any outcome	0	1
Repeated Measures ANOVA	all	0	1
	any outcome	1	2

Two trials are excluded from the table because the methods used were unclear from the published article, and another trial which performed a LOCF analysis using all patients is excluded because the proportion of missing data is unknown.
[a]Inclusion criteria: final outcome = analyses that include only individuals with final outcome, all = analyses which include all individuals, and any outcome = analyses which include individuals with ≥1 intermediate measurement or final outcome.
[b]1 trial imputed with the worst case value when dropout was due to death, otherwise imputed with LOCF.

proportions of missing outcomes (median 21%, IQR 9–31%) (Table 5). Three trials reported two sensitivity analyses. The most common form of sensitivity analysis was LOCF when the primary analysis adopted a complete case analysis.

Discussion

This review has identified serious weaknesses in the description of missing data and their handling in the reported analysis of randomized controlled trials in major medical journals, presumably with fairly strong statistical review policies; it is hard to imagine that the situation would be better in journals with less intensive statistical review. We recognize that a variety of techniques and exploratory analyses may have been performed and not reported because of space constraints in these journals, but there was no indication in the published papers that they had been conducted. We do not know if conclusions would have been different if such methods had been employed, but ascertaining that is one of the purposes of such methods. There was almost no use of modern missing data methods, and widespread use of a method (LOCF) that is typically not recommended. Below, we review recommendations for avoiding and handling missing data in randomized controlled trials.

Trial design

In most randomized controlled trials, the occurrence of missing data is deemed likely at the study design stage. Emphasis is frequently, and rightly, placed on the avoidance of missing responses: see, for example, the Cochrane review for strategies to increase response to postal questionnaires [18]. The use of secondary sources, for example, general practice notes, to obtain outcome data information can also be valuable when there are missing data from the primary source (e.g., patient questionnaires). Occasionally, there can be a trade-off between obtaining all data regardless of its reliability or having missing data [19].

When missing data are anticipated, the sample size should be inflated to ensure adequate power in the analyses. When possible, collecting interim measures of the outcome is desirable since it increases the number of individuals with at least some outcome data. Such a repeated measures design can make MAR assumptions more plausible [4].

Description of missing data

Trials in our survey followed the CONSORT statement [20] in reporting the numbers of patients with missing outcome data by treatment arm. An imbalance in the proportions missing between

Table 5 Description of trials performing a sensitivity analysis for missing data

Study	Outcome	Single/repeated outcome	No. of subjects	% missing	Primary analysis	Sensitivity analyses
Albert	Change in C-reactive protein levels	Repeated	2013	33	LOCF (not baselines)	LOCF (including baselines)
Bauer *et al.*	Incidence of venous thromboembolism	Single	1049	31	Complete case	Not stated
Brown *et al.*	Mean change in stenosis	Repeated	160	9	Complete case	Worst case value
Krakow	Scores on the nightmare frequency questionnaire	Repeated	168	41	LOCF (not baselines)	• Complete case • LOCF (including baseline)
Kroeke *et al.*	Change in SF-36 Mental Component Summary Score	Repeated	601	25	RMANOVA (if baseline interview completed)	• Worst case value for those with missing baseline • LOCF
MacKenzie *et al.*	Ratings of Laryngeal features	Repeated	204	35	Complete case	LOCF (baseline only)
Murray *et al.*	Perceptions in decision making	Repeated	205	9	Complete case	LOCF
Murray *et al.*	Perceptions in decision making	Repeated	112	9	Complete case	LOCF
Scott *et al.*	Anti-social behaviour in children	Single	141	22	Complete case	LOCF (baseline only)
Time investigators	Quality of life	Single	305	20	Complete case: missing values in questionnaire filled in	Complete case: lower thresholds for missing values in questionnaire
Wirth *et al.*	Weight loss	Repeated	1001	21	LOCF	Complete case
The writing group for the Activity Counseling Trial Research Group	Cardiorespiratory fitness	Repeated	874	10	RMANOVA	• Regression imputation • LOCF (baseline only)
Van Gool *et al.*	Deterioration in daily life in dementia	Repeated	168	8	Regression imputation	Complete case

RMANOVA = repeated measures analysis of variance.
LOCF = Last observation carried forward.

treatment arms is likely to cause bias where the outcome of interest may be associated with the risk of patient withdrawal [21].

Reasons for missing data are frequently collected and reported and are extremely valuable since they can be used to help justify the analysis assumptions. Investigators should try to capture as much information as possible regarding how each patient may have responded, since individuals who drop out for different reasons may need to be handled differently in the analysis. For example, in one trial 21% (214/1001) of obese people withdrew before a final weight reduction was recorded [22]. Reasons for withdrawal included lack of efficacy ($n = 25$), adverse event ($n = 47$), loss to follow-up ($n = 47$) and patient request ($n = 53$). The primary analysis imputed all missing values using the LOCF. The implicit assumption of zero weight loss from the point of discontinuation may be reasonable for patients who were lost to follow-up, but the patients who withdrew due to lack of efficacy are more likely to have returned to their pretrial weight and carrying the baseline value forward may be more appropriate [23].

Comparisons of baseline variables between treatment arms for those with observed outcome data indicate how the subjects with missing outcomes affect the randomization balance. Imbalance means that baseline-adjusted analyses are essential, but even these may not remove nonresponse bias. Comparisons of baseline data between subjects with observed and missing outcomes can be used to assess the plausibility of the MCAR assumption.

Principal analyses

Most trials use simple forms of analysis, typically excluding patients who do not have the outcome or imputing the missing outcomes with previously observed measurements. These methods of analysis are easy to implement but have numerous disadvantages. When an outcome is observed at only a single point in time, there are few options. Almost all of the trials reviewed excluded individuals with missing outcome data and performed a complete case analysis. This method is easy to implement but can produce biased treatment effects if the missing data are not MCAR. Even when a complete case analysis is not biased, it estimates the treatment effect among the subpopulation of patients who complete the trial, so the generalizability of the results may be impaired.

Imputation techniques aim to create a full dataset like that which would have been observed. An ad hoc approach is to impute with the worst case or best case value, but this very rarely leads to unbiased results for the treatment effects, and are often too extreme [6]. Also, these methods do not generally apply to quantitative outcomes: for example, it is hard to assign a "worst case" blood pressure. Another alternative is extreme case analysis, where patients lost to the group with better overall outcome are assigned a poor outcome, and those lost to the group with worse overall outcome are assigned a good outcome [24]. No trials in our study presented results from these procedures. Extreme case analyses can sometimes provide useful bounds on the effects of the missing data.

When interim measures of the outcome are collected, there is more information available to predict the missing primary outcomes. Yet, half of our trials did not use this extra information and the simple complete case analysis was applied. Most of the other studies adopted the LOCF method, which assumes the last available measurement for an individual is an unbiased representation of the missing value, without allowing for within subject variability or changes over time. The methods are claimed to be conservative [25] in nonprogressive conditions [26], but this is not necessarily the case when there are more missing data in one group or where selection bias may occur and operate differently between the two groups. As with all single imputation methods, its use understates the true uncertainty in the outcome. The LOCF approach to missing outcome data is rarely preferred and often not acceptable.

Only a small proportion of trials with repeated measures actually performed an analysis that made full use of all available data. Likelihood-based inferences such as repeated measures ANOVA [27] and multilevel modeling [28] can deal with incomplete (unbalanced) repeated measures data and are valid under missing at random provided the models are correctly specified. Generalized Estimating Equations [29] (GEEs) is also a technique in which all available data are used but is only valid under MCAR. By allowing for correlation between an individual's observations, these approaches implicitly obtain the expected outcome based on all available data from subjects with any intermediate measurements.

Regression imputation (single and multiple [30]) is based on the MAR assumption. In these analyses, an imputation model is built relating the primary outcome to covariates and possibly intermediate values of the outcome. The imputation model is fitted to the individuals with the observed outcome and used to predict the outcomes among subjects whose outcome is unobserved. Use of a single imputation [3], whether deterministic or stochastic, generally underestimates the standard errors [10]. Multiple imputation uses several stochastic imputations which gives valid standard errors (under MAR) that incorporate the uncertainty about the imputed value [31]. Multiple imputation can be implemented

in SOLAS [32], SPSS MVA [33], SAS proc MI [34] and NORM [35]. Missing baseline covariates may be handled in the imputation model by the missing indicator method or mean imputation. These methods may introduce bias in observational studies [36] but not in randomized controlled trials [2].

More sophisticated statistical techniques for handling missing data which are MNAR allow for the risk of patient withdrawal to be related to the patient outcome [13,37,38]. Such methods are not yet available in standard software packages.

Sensitivity analysis

We found that sensitivity analyses are infrequently used and typically involve only one or two alternative analyses. Trialists should examine the effect of different assumptions on the conclusions, and at the very least perform an analysis valid under MAR assumptions (i.e., not just MCAR). Sensitivity analyses should not share the same assumptions about missing data as the original analysis. For example, a randomized trial of statin therapy [39] measured C-reactive protein levels at baseline, 12 weeks and 24 weeks. The principal analysis of the change in C-reactive protein levels from baseline to 24 weeks included all patients with at least the baseline and 12-week measurements. Outcomes missing at 24 weeks were imputed by carrying forward the 12-week measurement. The sensitivity analysis additionally imputed the 24-week measurement, for those without the 12-week measurement, with the baseline value. This sensitivity analysis does not address the potential bias due to carrying observations forward, and a repeated measures analysis might have been used which would have been valid under the MAR assumption.

Summary of conclusions and recommendations

Trial design

- The potential occurrence of missing outcomes should be recognized at the trial design stage and measures taken to try to minimize them.
- Outcomes should be collected repeatedly, if possible, or secondary sources should be used to obtain outcomes , so that at least some data are available for all subjects. More frequent data collection increases the number of patients with outcomes nearer the final outcome and increases the plausibility of MAR assumptions.
- Reasons why individual patients fail to have completely observed data should be collected and used to inform missing data assumptions.

Reporting missing data

Trials should report descriptions of the missing data, such as:

- the difference in proportions missing between treatment arms;
- differences in key baseline characteristics between treatment arms in those with observed outcomes; and
- differences in key baseline characteristics between individuals with missing and observed outcomes.

Analyzing missing data

- Trials should aim to include in the analysis all individuals with any outcome data. For repeated measures, this will require methods of analysis such as multiple imputation or an appropriate repeated measures analysis, such as multilevel modelling [28].
- Patients with no data after baseline cannot easily be included in any analysis.
- LOCF is rarely appropriate.
- Patients who have dropped out for different reasons may need to be handled in different ways in the analysis.
- All methods of analysis have assumptions that cannot be fully justified from the data. It is important to state what the assumptions are and their motivation so that the reader can assess their plausibility.

Sensitivity analyses

- If a substantial proportion of outcomes are missing then formal sensitivity analyses should be reported [40].
- Sensitivity analyses should vary the primary assumptions made about the missing data enough to detect any important inadequacies in the assumptions made in the principal analysis.
- If journal space constraints that prevent full reporting of sensitivity analyses, their results should be reported in the text and the full analyses presented in electronic appendices.

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