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Missing data in trial based cost-effectiveness analysis: The current state of play

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Abstract

Aims:

To review missing data techniques used in randomised controlled trial (RCT) based cost-effectiveness analyses.

To examine: the influence of resource use collection methodology and study perspective on the amount of missing data, and whether missing data methodology improved over time.

To make suggestions on the reporting of missing data.

Methods:

Articles published 01/01/2003 to 31/03/2009 fulfilling the search criteria were selected from Science-Direct.com and bmj.com. The method/s of dealing with missing data, how resource use was obtained, study perspective, publication year and number of complete cases were extracted from each article.

Results:

The most popular primary analysis approach for the 88 articles included in the review was complete case (CC) analysis (31%). 16% did not mention any missing data approach. 22 articles conducted missing data sensitivity analysis, of these 77% included a CC analysis and 59% used multiple imputation. The percentage of articles using the CC approach as their primary analysis increased over time.

Only 30/88 articles reported the number of complete cases used in the cost-effectiveness analysis. Face-to-face or telephone interview produced the highest (82%) and questionnaire and medical records the lowest (60%) percentage of complete cases. As the perspective widened the percentage of complete cases decreased.

Conclusions:

The degree of missing data in cost-effectiveness analyses is often poorly reported and the methodology is often unclear. CC analysis, which may lead to inappropriate conclusions, is still the most popular approach and its use increased with time. Reporting of missing data sensitivity analyses would improve the transparency of articles.

Introduction:

The increasing use of trial based economic evaluations in the assessment of healthcare technologies has highlighted the need for appropriate methodological approaches to the handling of missing data. Missing data occurs in economic evaluations when: patient medical records are missing or incomplete; resource use questionnaires are not fully completed, or patients withdraw from the trial or cannot be contacted for interview.

Economic evaluations are prone to missing data. Cost, at any point in time, is the sum of individual components (e.g. inpatient care, primary care, medications) hence if one of these components is missing then the total cost will also be missing. The cumulative nature of cost (i.e. cost is often collected at different time points throughout the trial) exacerbates this issue.

If missing data is ignored and analysis is conducted on patients without missing cost-effectiveness data (complete case analysis) then bias may be introduced, in that those with complete data may differ from those with incomplete data. Secondly, there may be a loss of power through a reduction in the sample size available for analysis. The article by Briggs et al [1] was one of the first articles to highlight the issue of missing data within the field of health economics. The article explained the different mechanisms of missingness, the problems with the naïve approaches being used, and what approaches should be used instead.

There are three types of missing data mechanisms [2]: Missing completely at random (MCAR), Missing at random (MAR) and Missing not at random (MNAR). If data is assumed to be MCAR then the probability that the data is missing does not relate to the characteristics of the individual, hence the cases with the missing data can be seen as a random sample of the population. If the data is assumed to be MAR then the probability that the data is missing is related to the observed variables of the individual. Finally, if the data is assumed to be MNAR then the probability that the data is missing relates to both observed variables and unobserved characteristics of the individual.

The most common ways to deal with missing data are as follows:

A. Complete case (CC) analysis, whereby individuals are only included in the analysis if they have complete information on all required data.
B. Last Value Carried Forward (LVCF), in this case the missing value for the variable at time t is replaced by the value for the variable at time t_{-1}
C. Mean imputation, in this approach the missing values are replaced with the mean value of the variable in question.
D. Regression imputation also known as conditional mean imputation, whereby the predicted mean from a regression model, conditioned on observed variables of the individual, is used to replace the missing values.
E. Multiple imputation, this approach is designed to reflect the uncertainty surrounding the missing data through a two-stage process. Initially multiple copies of the original dataset are created in which the missing data is replaced by imputed values which are derived from the predictive distribution based on the observed data. Once the datasets are created the same analysis is applied to each dataset. The estimates from each of the datasets are then averaged together, and the total variance is calculated using Rubin's rules [3]

Validity of any of these approaches depends on the mechanism which causes missing data. Of these methods, CC analysis will be an unbiased approach if the data is MCAR, CC analysis may also be unbiased if the outcome data is MAR and all the variables related to missingness are included in an analysis model. This would then mean that within each strata, defined by the covariates, of the outcome variable the missing data would have the same distribution as the observed data. For example, if within a hospital setting, whether total cost data was missing was only dependent on length of stay and this was available for almost all the patients, then a complete case analysis including length of stay as a covariate in the model would be unbiased. However, if the variable

related to both outcome and missingness is not included in the model, then complete-case analysis will be biased.

If the outcome of an individual does not change over time then LVCF will be a valid approach. If there are changes over time, then even if the data is MCAR, LVCF will be biased. Mean imputation will only be unbiased if the data are MCAR. Regression imputation will be unbiased if the data are MAR and all variables related to missingness and variables related to the value of the variable with missing data are included in the regression model. However, each of these three methods (LVCF, mean imputation and regression imputation) will under-estimate the uncertainty associated with each effect estimate, and thus under-estimate standard errors.

Multiple imputation will be approximately unbiased (as in the CC analysis) if, within each strata (defined by the near fully observed covariates included in the multiple imputation model) of the variables of interest, the distribution of the missing data is the same as the observed data. However, if such strata cannot be created because the missing data depends on unobservable characteristics of the patients (i.e. MNAR) then in general multiple imputation will be an invalid approach. Multiple imputation allows the bringing in of additional variables which contain information about the missing data in order to create these strata. In the example above, where whether total cost data was missing was only dependent on length of stay, inclusion of length of stay in an analytic model relating total cost to intervention arm would be undesirable (since costs are likely to be strongly dependent on length of stay). However, inclusion of length of stay in a multiple imputation model would be straightforward. Additionally multiple imputation reflects the uncertainty surrounding the missing values which is not achieved through conditional or mean imputation.

Other less common appropriate approaches assuming the data is MAR include using maximum likelihood estimation, [4] random effects (mixed) models (if you have longitudinal data) [5] and inverse probability weighting (where first the probability of being missing is modelled and then the complete-case analysis is conducted but is weighted by the probability of being a complete case)

This article reviews the techniques that have been used to deal with missing data in economic evaluations since the publication of the Briggs article in 2003. The data abstracted from the articles are used to examine possible influences on missing data in terms of how resource use is obtained and the perspective of the study. We also evaluate whether more recent articles use more appropriate methods for dealing with missing data. Suggestions are also given on how missing data should be reported in trial based economic evaluations in order to aid the transparency of articles.

Methods:

In order to review missing data methods in trial based cost effectiveness analyses, search engines on two online full-text journal repositories were utilised. On both websites the search ran from 1st January 2003 until 31st March 2009.

1) On Science-Direct.com (with access to >2,500 journals) we searched for the terms ("cost effectiveness" or "economic evaluation") and "missing data" and "trial" and ("randomised" or "randomized") anywhere in the full text of the article.
2) On bmj.com which accesses all High Wire Press hosted journals (> 1,250 journals), the search engine was not as comprehensive, therefore 4 different searches were performed in which the following terms had to be present anywhere in the article:
    a. "cost effectiveness" AND "missing data" AND "randomised" AND "trial"
    b. "cost effectiveness" AND "missing data" AND "randomized" AND "trial"
    c. "economic evaluation" AND "missing data" AND "randomised" AND "trial"
    d. "economic evaluation" AND "missing data" AND "randomized" AND "trial"

One author (SN) examined the abstract of each article and any article that was not an economic evaluation of a randomised controlled trial was excluded, as were articles that did not use individual patient data. The remaining articles were read in their entirety and for those papers

which were cost-effectiveness analyses alongside randomised controlled trials; the method of dealing with missing data was extracted.

In addition, information on how resource use was obtained, the perspective of the study, the year of publication and the number of complete cases used in the cost-effectiveness analysis was extracted from the articles to examine the following hypotheses:

- The way resource use is obtained will affect the amount of missing data.
- The wider the perspective, the greater the amount of missing data.
- The more recent the year, the more appropriate methods for dealing with missing data.

For a number of evaluations, in order to simplify the analysis, any missing data method used by less than four articles was reclassified as "other".

During the abstraction of data from the articles when an article contained both a multiple imputation and a complete case analysis then the two sets of results were examined to see if the type of analysis made a difference to the results. In articles that reported missing data sensitivity analyses for costs, then a difference was defined as whether the statistical significance/non significance, determined by statistical testing/confidence intervals, between the arms of the trial remained the same in the two analyses.

In articles that reported missing data sensitivity analyses in terms of cost-effectiveness a difference was defined as: the intervention with a positive net monetary benefit became negative; or an Incremental Cost Effectiveness Ratio (ICER) went from below £20,000 per additional Quality Adjusted Life Year (QALY) to greater than £20,000 or becomes dominated; or a Cost Effectiveness Acceptability Curve (CEAC) showed that the intervention no longer had a probability of greater than 50% of being cost-effective over a range of willingness to pay variables.

Results:

Study selection

In the ScienceDirect.com search 244 articles were found, after review of the abstract 41 articles were read in full. The bmj.com search identified 1415 articles (approximately half of which were duplicates within the bmj search). After abstract review, 111 of these articles were read in their entirety.

Of the 152 full text articles, 88 were cost-effectiveness analyses of randomised controlled trials and were included in the review. Of the remaining 64 articles, 42 were cost, cost consequence or cost minimisation studies, 5 studies were based on modelling or did not use individual patient data, 10 were not randomised controlled trials and 7 articles were the main trial effectiveness results paper.

Methods for dealing with missing data

Table 1 shows how missing data was dealt with in the primary cost-effectiveness analyses. The majority, 27/88 (31%), of the articles conducted a complete case analysis, 9/88 (10%) used mean imputation, and conditional imputation was used by 8/88 (9%) of articles as was multiple imputation. 14/88(16%) of articles did not mention any missing data method.

Table 2 shows how missing data was dealt with by whether a sensitivity analysis was conducted (the SA group) or not (the NSA group). In the NSA group (n=66) 19/66 (29%) of these articles only conducted a complete case analysis, and a further 12/66 (18%) articles did not mention any approach in relation to dealing with missing cost data. When an attempt was made to impute data, mean imputation was the most popular approach (9/66;14%).

In the 22 articles that performed one or more sensitivity analyses, 77% (17/22) included a complete case analysis, 59% (13/22) carried out multiple imputation, 23% (5/22) conditional imputation and 23% (5/22) mean imputation.

Ten articles reported results from both multiple imputation and complete case analysis. Four of these articles only reported these analyses for the costs. In three articles, the method of dealing with missing data, did not affect the interpretation of results. In one article the costs in one of the arms reduced by over two- thirds, but there were no confidence intervals shown or statistical analyses conducted to determine whether this changed the statistical interpretation of study findings. The remaining six articles reported different missing data analyses in terms of cost-effectiveness. The same intervention remained cost effective in three of these articles, it differed in two [6], [7], and in one paper there was insufficient information for this to be determined.

The prevalence of missing data in cost-effectiveness analyses

It was only possible to abstract the actual number of complete cases used in the cost effectiveness analysis for 30 of the 88 articles reviewed. The results in tables 3 and 4 are therefore based on these 30 articles.

Table 3 shows the estimated mean percentage of complete cases by method of collecting resource use. The use of face to face or telephone interview produced the highest (82%) and the use of questionnaire and medical records produced the lowest (60%) estimated mean percentage of complete cases.

Table 4 shows the estimated mean percentage of complete cases by perspective of evaluation. The percentage of complete cases decreases as the perspective widens with the articles from the societal perspective having the lowest proportion of complete cases.

In order to examine whether methods of dealing with missing data changed over time, the manuscripts were allocated into two groups by year of publication, 2003-2005 and 2006-2009. Figure 1 shows that overtime there was an increase in use of the complete case approach as the primary analysis (24% to 35%) and in all articles (26% to 48%). There was also a decrease in the use of mean imputation as a primary analysis (15% to 7%) and overall (21% to 13%). This increase in

the use of complete case analysis is echoed when the manuscripts were further allocated to the NSA group and the SA group (Table 5). In 2006-9 80% of articles which included a sensitivity analysis conducted a complete case analysis compared with 57% in 2003-5. Further the percentage of articles which incorporated a sensitivity analysis increased overtime from 21% (7/34) to 28% (15/54).

Discussion:

The degree of missing data in cost-effectiveness analysis has been shown to be poorly reported, and the methods used to handle missing data are often unclear. The majority of studies do not report a sensitivity analysis which would allow the reader to judge whether the method for handling missing data affected the conclusions. Complete case analysis is still the most popular approach for cost-effectiveness analyses and its use has increased with time.

If complete case analysis is the only approach that is used and the missing data is not MCAR then bias may occur because those with complete data may differ from those with incomplete data. Only 7 of 19 articles that only used complete case analysis discussed whether there was any evidence of bias in their data. One of these seven articles made the assumption of MCAR, they made this assumption based on the values for predictor covariates being similar between individuals included and excluded in the analysis [8] A further four studies mentioned that there were no differences between individuals who did or did not have missing data [9] [10],[11, 12], and two mentioned that there was some evidence of bias [13],[14].

Even if the data is MCAR there will be a loss of statistical power due to cases being dropped from the final analysis. Of the 9 articles which only used complete case analysis and which reported the number of complete cases for the cost-effectiveness analysis, only one had less than 5% missing data [14], and would therefore be unlikely to suffer from loss of power or bias because of the virtually complete dataset.

The technique of mean imputation was the most popular approach for imputing missing data in studies that did not conduct a sensitivity analysis for missing data methods. Using mean imputation in cost-effectiveness analysis may simply be unrealistic due to the discrete nature of the resource use data. For instance the mean number of hospitalisations in a study might be 0.5, but no patient will have 0.5 of a hospital admission. Furthermore the use of mean imputation or any deterministic single imputation will lead to an attenuated correlation structure of the data and an underestimate of the variance for that variable, resulting in confidence intervals that are too narrow. Similarly, regression imputation (conditional mean imputation) that was used in 11 articles will also understate uncertainty.

In the group of articles that did conduct sensitivity analyses, multiple imputation was the most popular way of imputing missing data. Multiple imputation is complex and can be a "black box" for reviewers and readers trying to assess the validity of study findings. To aid transparency, it would be appropriate to outline what equations were used in the imputation process. This occurred in only 7 of the 16 articles that used multiple imputation. Other issues such as which multiple imputation procedure and software is used (5 used the propensity method[15], 3 used chained equations [16], 3 used data augmentation and 5 did not specify their approach), and how confidence intervals/Cost Effectiveness Acceptability Curves (CEACs) are created from the multiple imputed datasets (5/16 articles) would also aid the transparency of approach. Only 2 articles addressed all the above aspects [6], [7]. These guidelines for transparency reflect the recent article [17] on how to report multiple imputation analyses in epidemiological and clinical research.

Whilst it is concerning that 14/88 articles did not mention how missing data in relation to costs was analysed, this is probably the tip of the iceberg. The search strategy we used would not have picked up studies that did not mention the term "missing data".

The examination of different issues in relation to the amount of missing data was hampered because only 30 of 88 articles actually reported the number of complete cases for the cost effectiveness. This information was often not available because the number of complete cases was reported for each time point but not cumulatively (e.g[18],[19]) or articles reported that there was only a small proportion of missing data (e.g.[20]) with no actual figures given. Another common issue was that for each component of resource use complete cases were given, but not an overall figure (e.g. [21], [22]). The CONSORT statement on improving the quality of reporting of randomised controlled trials emphasizes the importance of stating the numbers of patients included in the analysis [23, 23]. But this issue has received less attention in guidelines for reporting economic evaluations [24]

The results in relation to these different issues must therefore be treated with caution. The limited data suggest that as the perspective of the study widens so does the amount of missing data. This may be in part a result of the need to use questionnaires or diaries to obtain information on patient's direct and indirect costs, rather than relying solely on medical records. This presents a dilemma for Governmental decision makers who wish to take a broad perspective in policy, but may end up with less precise or even more biased cost-effectiveness data if they do so.

Overtime improvements in reporting missing data have been the increase in articles using a missing data sensitivity analysis, and the use of the complete case analysis as one of these approaches. Furthermore, there has been a decline in the use of mean imputation. The main issue remains the increased use of compete case analysis as the only approach to analysing data.

The sciencedirect.com and bmj.com search engines were used rather than search engines such as PubMed, as unless the article is methodological, then it is unlikely that the term "missing data" will be put as a key word or included in the abstract. This was evidenced by a Web of Knowledge search using the same search criteria which only produced 37 results.

In research, where missing data could lead to a wrong decision being made, then examining different approaches to missing data through sensitivity analysis would be appropriate. Complete case analysis should be one of the approaches used and the numbers in the complete case cost-effectiveness analysis should be stated to aid transparency. The examination of the results from the ten articles which reported analyses using both multiple imputation and complete cases showed that in two of these cases [6] and [7] a potential wrong decision may have been made.

This review article has illustrated that missing data in relation to cost-effectiveness analyses of randomised controlled trials is still a much-overlooked issue. Complete case analysis is still the most common way of reporting results. Given the high proportion of missing data common in economic evaluation this suggests that many conclusions are based on imprecise, possibly biased, economic evidence.

However, the best way to deal with missing data is not to have it at all. Further work in questionnaire design, an increased use of medical records and other routine sources, may be a way forward in this respect.

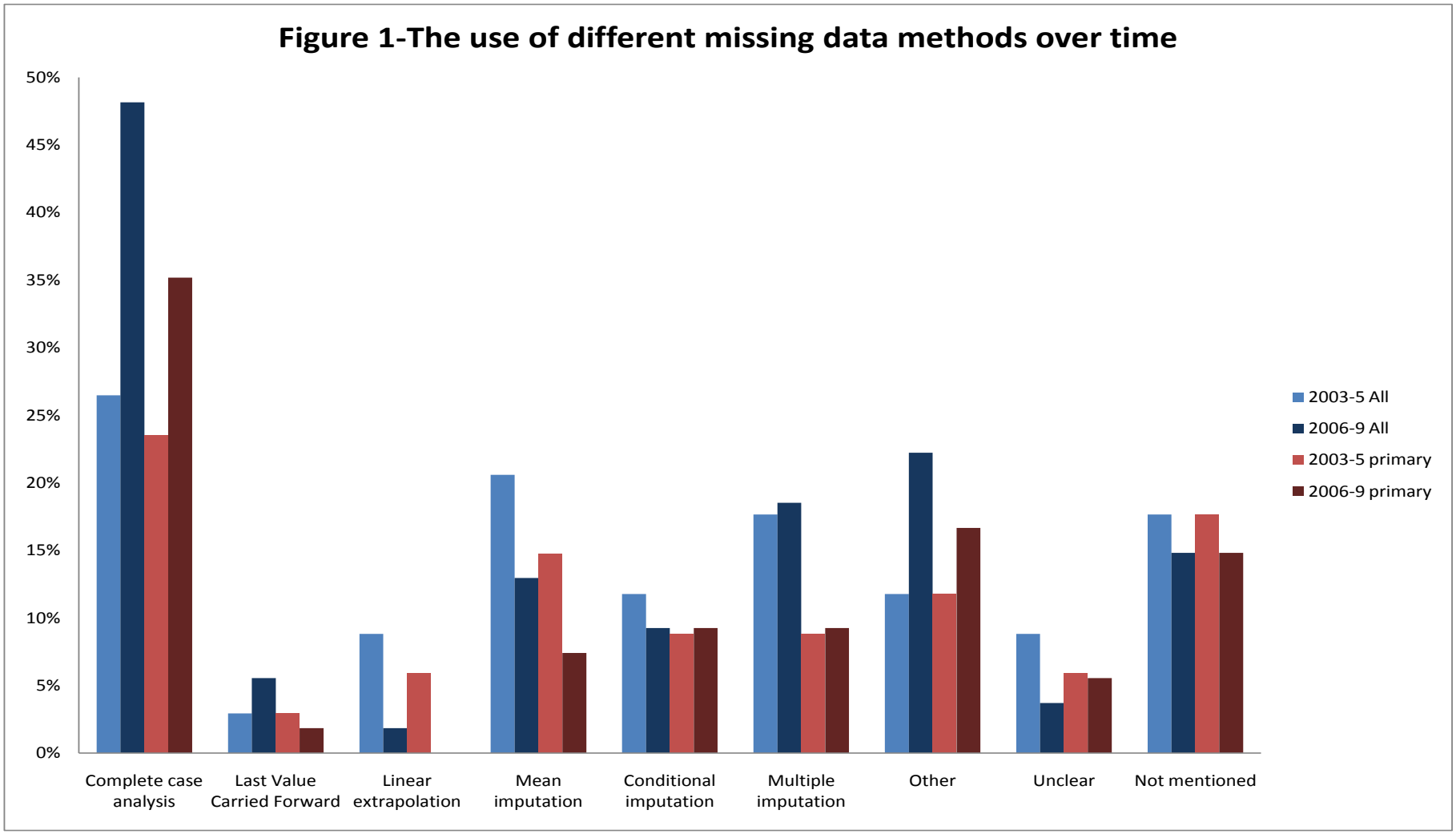
Figure 1-The use of different missing data methods over time
50%
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
Complete case analysis
Last Value Carried Forward
Linear extrapolation
Mean imputation
Conditional imputation
Multiple imputation
Other
Unclear
Not mentioned
2003-5 All
2006-9 All
2003-5 primary
2006-9 primary

Table 1 – Methods for dealing with missing data in the primary analysis

	Number (%) of articles using each missing data approach in the primary analysis
A	
Complete case analysis	27 (31%)
B	
Last Value Carried Forward	2 (2%)
Linear extrapolation	2 (2%)
C	
Mean imputation	9 (10%)
D	
Conditional imputation	8 (9%)
E	
Multiple imputation	8 (9%)
F (Combined methods)	
Mean imputation and conditional imputation	2 (2%)
Last Value Carried Forward and mean imputation	1 (1)%
Multiple imputation and survival analysis and assumed zero for blanks in questionnaire	1 (1%)
Poisson imputation and uniform distribution imputation and multiple imputation	1 (1%)
Weighted least squares following linear extrapolation	1 (1%)
G (other)	
Mixed model with repeated measures	1 (1%)
Maximum Likelihood estimation using the EM algorithm	1 (1%)
2-part regression	1 (1%)
Available case analysis	1 (1%)
Assumed zero for blanks in questionnaire	2 (2%)
Patient year approach	1 (1%)
H (Unclear)	
Unclear	5 (6%)
Not mentioned	14 (16%)
Total	88 (100%)

Table 2 – Methods for dealing with missing data in articles which did and did not conduct a sensitivity analysis

	Number of approaches to missing data (% of articles using each approach)	
	NSA group	**SA group**
Complete case analysis	19 (29%)	17 (77%)
Last Value Carried Forward	1 (2%)	3 (14%)
Linear extrapolation	2 (3%)	2 (9%)
Mean imputation	9 (14%)	5 (23%)
Conditional imputation	4 (6%)	5 (23%)
Multiple imputation	3 (5%)	13 (59%)
Other	11 (17%)	10 (23%)*
Unclear	5 (8%)	0 (0%)
Not mentioned	12 (18%)	2 (9%)
Total articles (analyses)	66 (66)	22 (57)

*In the SA group 10 of the "other" approaches came from 5 articles

Table 3 – The estimated mean percentage of complete cases by method of collecting resource use

How resource use collected	**Number of articles**	**Mean percentage of complete cases (range)**
Patient self reported Questionnaire	4	74 (65-80)
Diary only	5	62 (34-80)
Face to face /telephone interview	4	82 (76-89)
Medical records/administrative system	4	79 (71-88)
Patient self reported Questionnaire and medical records	7	60 (48-71)
Medical records and interview	1	68
Not mentioned	5	85 (69-99)

Table 4-The estimated mean percentage of complete cases by perspective of evaluation.

Perspective of evaluation	Number of articles	Mean percentage of complete cases (range)
Health Service	6	72% (65%-80%)
Societal	16	67% (34%-89%)
Other	4	81% (76%-99%)
Not mentioned	4	84% (80%-93%)

Table 5 Approaches to missing data over time by whether an article conducted a sensitivity analysis

	2003-2005				2006-2009			
	NSA group		SA group		NSA group		SA group	
Complete case analysis	5	19%	4	57%	14	36%	12	80%
Last Value Carried Forward	0	0%	1	14%	1	3%	2	13%
Linear extrapolation	2	7%	1	14%	0	0	1	7%
Mean imputation	5	19%	2	29%	4	10%	3	20%
Conditional imputation	2	7%	2	29%	2	5%	3	20%
Multiple imputation	2	7%	4	57%	1	3%	9	60%
Other	3	11%	1	14%	8	21%	4	27%
Unclear	3	11%	0	0%	2	5%	0	0%
Not mentioned	5	19%	1	14%	7	18%	1	7%
Total number of articles	27		7		39		15	

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