**Increased transparency was required when reporting imputation of primary outcome data in clinical trials**

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**Objective:** To explore the transparency of reporting primary outcome data within randomised controlled trials (RCTs) in the presence of missing data.

**Study Design/ Setting:** A cohort examination of RCTs published in the four major medical journals (NEJM, JAMA, BMJ, Lancet) in 2013 and the first quarter of 2018. Data was extracted on reporting quality, the number of randomised participants and the number of participants included within the primary outcome analysis with observed or imputed data.

**Results:** 91/159 (57%) of the studies analysed from 2013 and 19/46 (41%) from 2018 included imputed data within the primary outcome analysis. Of these, only 13/91 (14%) studies from 2013 and 1/19 (5%) studies from 2018 explicitly reported the number of imputed values in the CONSORT diagram. Results tables included levels of imputed data in 12/91 (13%) studies in 2013 and 4/19 (21%) in 2018. Consequently, identification of imputed data was a time-consuming task requiring extensive cross-referencing of all manuscript elements.

**Conclusion:** Imputed primary outcome data is poorly reported. Participant flow diagrams frequently reported participant status which does not necessarily correlate to availability of data. We recommended that the number of imputed values are explicitly reported within CONSORT flow diagrams to increase transparency.

## Keywords: Missing data, retention, imputation, reporting transparency, CONSORT

**What is New?**

* CONSORT diagram and results tables rarely contained explicit information of the levels of imputed data within the primary outcome analysis.
* Many studies reported participant status at relevant time points rather than the availability of data.
* Extensive cross referencing of all aspects of the manuscript and supplementary material was often required to identify levels of imputed data.
* Further refinement of the CONSORT is recommended to encourage explicit reporting of the number of participants included in the primary analysis with imputed rather than observed data.

## Background:

Randomised controlled trials (RCTs) are the gold standard of research evidence due to their potential to limit bias when assessing the effects of treatment. Intention to Treat (ITT) is the recommended approach for analysing RCTs in order to prevent overoptimistic estimates of treatment effect[1](#_ENREF_1), [2](#_ENREF_2) and to preserve the balance created at randomisation.[3](#_ENREF_3) ITT requires all randomised participants to be included in the analysis, according to the group they were assigned, ignoring any subsequent deviations to the treatment regime or the study protocol.[2](#_ENREF_2) However, it is rare that every randomised participant will have outcome data available for analysis requiring these participants with missing data to be excluded entirely from the analysis or included with imputed values.[4](#_ENREF_4) Understanding the numbers and reasons why participants are excluded from the analysis or are included with imputed data is essential to assess the reliability of trial results and to support the design of future trials.[5-7](#_ENREF_5)

Missing data within a clinical trial may introduce bias. The potential for bias is dependent on the mechanism causing the data to be missing but also the analytical methods applied.[8](#_ENREF_8) Prevention of missing data is optimal but where this is not possible various approaches may be used to reduce bias and impute data for unobserved values. Analysis of trial data with missing values requires careful planning and attention.[9](#_ENREF_9) To support their evaluation of the evidence being reported, it is important that readers of clinical trials are provided with information regarding how many participants have observed data values and how many have values that have been imputed.[10](#_ENREF_10)

In 1996, the CONSORT statement was published to improve reporting standards for RCTs to aid readers in judging the reliability and validity of trial findings. The statement has since undergone revisions in 2001 and 2010 and is now embedded within the clinical trials community, with many journals making the recommendations a mandatory requirement for manuscript submission. A core part of CONSORT is ensuring that readers are able to understand the flow of trial participants from being assessed for eligibility, through randomisation and on to analysis of their outcome data. As such, every manuscript reporting the results of an RCT should include a participant flow diagram. Within this diagram, the numbers of participants who have been excluded from the analysis along with associated reasons should be reported along with the number analysed.[11](#_ENREF_11) While CONSORT recommends reporting post randomisation ‘losses’ in the flow diagram and the manuscript, whether this extends to explicit reporting of participants who are included in the analysis with imputed value is unclear.

Studies have looked at the overall levels of missing data within trials[10](#_ENREF_10), [12-14](#_ENREF_12), the reporting quality around handling of missing data [10](#_ENREF_10), [15-17](#_ENREF_15) and the appropriateness of imputation models[18-20](#_ENREF_18). However, to our knowledge, the transparency of reporting imputed primary outcome data frequency within participant throughput has not been assessed.

Our aim is to assess the transparency of reporting imputed values within the primary analysis of RCTs published in four major medical journals in 2013 and to compare this to a more recent cohort of publications in 2018.

## Methods:

A cohort examination of published randomised control trial reports was undertaken across two time periods.

### Literature search

Primary reports of parallel, two-arm RCTs published in four major medical journals (BMJ, New England Journal of Medicine, The Lancet and JAMA) in 2013 and the first quarter of 2018 were identified using the Cochrane Highly Sensitive RCT search strategy in MEDLINE (Ovid)[21](#_ENREF_21) (Supplementary Table 1). Publications from 2013 were originally identified as part of a wider project on missing data. Publications from 2018 were subsequently selected as this represented a five-year gap. Searches were run on the 11/02/2014 and 02/10/2018. Phase 1 and Phase 2 trials were excluded.

Article abstracts and titles were screened for eligibility by one author (AK). Any uncertainties were discussed with a second reviewer. Full texts were obtained for all potentially eligible articles.

### Data Abstraction.

As part of a wider project on reported reasons for missing data, the CONSORT flow diagram, text, results’ tables and supplementary material of eligible articles were cross-referenced to identify missing data for the main analysis of the primary outcome. Where there were potential discrepancies between different elements of the manuscript, the primary outcome result tables were used if they provided sufficient detail on missing outcome data.

Data was extracted independently by paired reviewers (AK, NB, ARH). Disagreements were resolved through discussion, or with a third party (CG) where necessary. Authors of eligible articles were not contacted.

Assessment considered descriptions of the primary outcome, the primary analysis population and the analysis methods in order to determine the use and likely availability of participant outcome data. For each trial, data were extracted on the number of randomised participants that were included in the analysis but their primary outcome data was not available, and the number of participants where it is was uncertain as to whether outcome data were available.

Data were also extracted on the number of randomised participants who were excluded from the primary analysis population. This was added to the number of participants for whom imputed data had been used to give an overall figure of missing data per trial.

Data collected from secondary sources (e.g. medical records or sleep diaries when actiograph measures were corrupted) and data missing from participants who did not reach follow-up points due to early study termination were not considered to be imputed.

To simplify data extraction and analysis, the following approaches were adopted:

* Where articles reported co-primary outcomes of safety and efficacy, we used the efficacy outcome only. For other co-primary outcomes, data were extracted on the first outcome mentioned.
* For studies using multiple time points in the primary analysis, we assessed levels of imputation at the final time-point.
* Manuscripts were searched to ascertain whether participant follow up continued if the trial intervention was either not received or stopped prematurely. Where no contradictory data was available, participants described as ‘withdrawn’ were assumed to have stopped follow up.
* Time to event data that was censored for reasons other than the end of the study, attainment of the primary outcome event or competing risk (as defined in the methods section) were considered to be attrition and were categorised as imputed data for the purposes of this study.

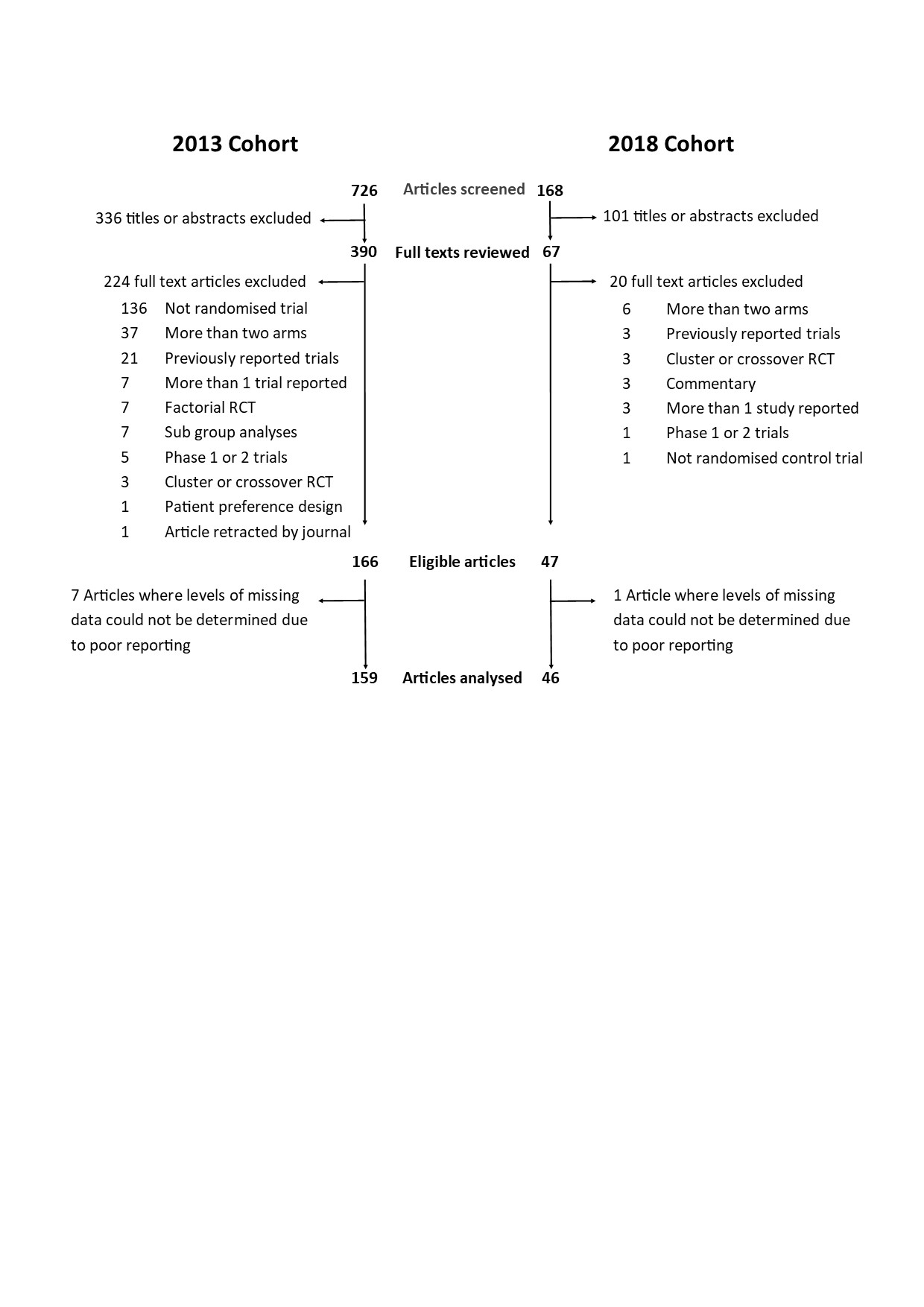
Eligible articles were assessed for compliance with the recommended guidelines for the CONSORT participant flow diagram (reporting of the numbers assessed for eligibility, randomised, receiving and completing treatment, completing follow up and included in the main analysis). The transparency of reporting imputed data was assessed by noting whether information on the number of participants included in the analysis with imputed outcomes was: explicitly reported in the CONSORT flow diagram along with the number analysed; whether it was identified by reviewing all elements of the CONSORT flow diagram; or whether it was identified from the wider article including any supplementary material. Whether a RCT reported levels of imputed data in its results’ tables was also extracted.

Data collection questions and guidelines were piloted on a small selection of papers (CG, AK) before review from co-authors.

Data was analysed in SAS 9.4 and descriptive statistics were used to report the analysis of cohort characteristics, the level of imputed data across the cohort of trials and reporting quality. Medians and interquartile ranges were reported for continuous data, proportions and percentages for dichotomous variables.

## Results:

The searches returned 726 articles for 2013 and 168 for 2018, of which 166/726 (23%) and 47/168 (28%) met eligibility criteria. (Figure 1).

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***Figure 1: Flow diagram of included studies.***

Trials in both cohorts covered a range of health categories with cardiovascular, infection, cancer and respiratory being the most common (Table 1). Most of the trials recruited adults (136/166, 82% in 2013 and 39/47, 83% in 2018) of both sexes (151/166, 91% and 41/47, 87%) and evaluated treatment interventions (140/166, 84% and 39/47, 83%). The median number [IQR] of randomised participants was similar in both cohorts (525 [253, 1374] in 2013 and 570 [254, 1638] in 2018). 74/166 (45%) trials in 2013 and 25/47 (53%) trials in 2018 adjusted their sample size calculations for missing data using predictions of between 3% and 35% and 3% and 25% respectively. 145/166 (87%) studies in 2013 and 39/47(83%) in 2018 described their analysis approach as either ‘Intention to Treat’ or ‘Modified Intention to Treat’.

|  |  |  |
| --- | --- | --- |
| Cohort Characteristics | 2013  (n=166)  No. (%) | 2018  (n=47)  No (%) |
| **Health Category** |  |  |
| Cardiovascular | 35 (21) | 6 (13) |
| Infection | 20 (12) | 6 (13) |
| Cancer | 16(10) | 7 (15) |
| Respiratory | 14 (8) | 6 (13) |
| Reproductive Health and Childbirth | 13 (8) | 4 (9) |
| Blood | 12 (7) | 2 (4) |
| Metabolic and Endocrine | 8 (5) | 1 (2) |
| Mental Health | 7 (4) | 5 (11) |
| Stroke | 7 (4) | 3 (6) |
| Musculoskeletal | 6 (4) | 3 (6) |
| Oral and Gastrointestinal | 6 (4) | 1 (2) |
| Inflammatory and immune system | 6 (4) | 0 (0) |
| Other | 16 (10) | 3 (6) |
| **Recruitment Population** |  |  |
| Adult only | 136 (82) | 39 (83) |
| Children only | 17 (10) | 4 (9) |
| Adults and children | 7 (4) | 3 (6) |
| Pregnant mothers/ in utero | 6 (4) | 1 (2) |
| **Recruitment Gender** |  |  |
| Mixed | 151 (91) | 41 (87) |
| Female only | 10 (6) | 6 (13) |
| Male only | 5 (3) | 0 (0) |
| **Intervention Aim** |  |  |
| Treatment | 140 (84) | 39 (83) |
| Prevention | 24 (14) | 8 (17) |
| Diagnostic | 1 (1) | 0 (0) |
| Other | 1 (1) | 0 (0) |
| **Intervention Type** |  |  |
| Drug | 80 (48) | 25 (53) |
| Other | 35 (21) | 7 (15) |
| Medical device | 28 (17) | 5 (11) |
| Surgical | 12 (7) | 8 (17) |
| Behavioural/educational | 6 (4) | 2 (4) |
| Diagnostic test | 2 (1) | 0 (0) |
| No intervention | 2 (1) | 0 (0) |
| Physical | 1 (1) | 0 (0) |
| **Blinding** |  |  |
| Open | 85 (51) | 29 (62) |
| Blinded | 75 (45) | 17 (36) |
| Unclear | 6 (4) | 1 (2) |
| **Primary outcome data** |  |  |
| Binary | 61 (37) | 16 (34) |
| Time to event | 51 (31) | 15 (32) |
| Continuous | 46 (28) | 11 (23) |
| Event rate | 6 (4) | 3 (6) |
| Unclear | 2 (1) | 2 (4) |
| **Reporting of primary outcome\*** |  |  |
| Patient | 39 (23) | 2 (4) |
| Healthcare/ clinical / research staff | 109 (66) | 39 (83) |
| Lab | 52 (31) | 14 (30) |
| Technology | 42 (25) | 4 (9) |
| Unclear | 2 (1) | 1 (2) |
| Other | 0 (0) | 1 (2) |
| **Location of primary outcome assessment\*** |  |  |
| Outpatient | 140 (84) | 42 (89) |
| Inpatient | 44 (27) | 9 (19) |
| Unclear | 11 (7) | 1 (2) |
| **Primary analysis populationX** |  |  |
| Intention to treat | 119 (72) | 30 (64) |
| Modified intention to treat | 26 (16) | 9 (19) |
| Not specified | 14 (8) | 6 (13) |
| Per protocol | 4 (2) | 1 (2) |
| Other | 2 (1) | 1 (2) |
| Complete case analysis | 1 (1) | 0 (0) |

***Table 1: Cohort Characteristics***

***Notes:*** *\* Answers were not mutually exclusive. x This is the primary analysis population as described in the article. We have not attempted to verify the approach or explore definitions.*

### Reporting of participant flow within the CONSORT diagram

Only one article in 2013 did not include a CONSORT flow diagram. The number of randomised participants was reported in all diagrams, but only 62/165 (38%) in 2013 and 19/47 (40%) in 2018 reported the numbers completing follow up (Table 2). Whilst the CONSORT flow diagram included the number of participants analysed in 126/165 (77%) and 40/47 (85%) of studies in 2013 and 2018 respectively, this was different to the denominator in the primary outcome results’ tables in 16/165 (10%) studies in 2013 and 3/47 (6%) in 2018 (Supplementary Table 2).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Recommended elements to be reported in the CONSORT flow diagram** | **No of trials reporting the element (%)** | | | |
| **2013 cohort (n=165) a** | | **2018 Cohort (n=47)** | |
| **Yes** | **Unclear** | **Yes** | **Unclear** |
| Number screened | 117 (71) | 3 (2) | 36 (77) | - |
| Number eligible | 115 (70) | 4 (2) | 34 (72) | - |
| Number randomised | 165 (100) | - | 47 (100) | - |
| Number received treatment | 111 (67) | 1 (1) | 34 (72) | - |
| Number completed treatment b | 62 (38) | 4 (2) | 19 (40) | 2 (4) |
| Number completed follow up | 103 (62) | 23 (14) | 32 (68) | 6 (13) |
| Number analysed | 126 (76) | 3 (2) | 40 (85) | - |

***Table 2: Frequency of studies reporting different elements of the CONSORT participant flow diagram***

***Notes:*** *Data were extracted on inclusion of the key reporting requirements listed in CONSORT. Accuracy and consistency of numbers with the remainder of the manuscript was not assessed in this analysis. a1 study did not include a CONSORT flow diagram. b 22/99 of those not reporting completion of treatment were perceived to have tested a one-off treatment.*

### Identification of imputed values.

In 7/166 (4%) articles in 2013 and 1/47 (2%) in 2018, missing data could not be quantified due to conflicting information that could not be resolved from the article and its supplementary materials or because it was not possible to determine which attrition values were relevant for the primary outcome (Supplementary Table 3). Consequently, we were unable to include these papers in the following analyses.

Missing primary outcome data were identified in 141 /159 (89%) of the remaining trial reports from 2013 and 38/46 (83%) from 2018. Within these studies the median percentage of randomised participants with missing data was 5.4% [1.5, 10.7] in 2013 and 2.6% [0.3-15.4] in 2018. Only one trial explicitly confirmed there was no missing outcome data.

In the 2013 cohort, 91/159 (57%) trials reported use of imputation to include participants for whom the primary outcome had not been observed. For those 91 studies the median percentage of randomised participants per trial that were included in the analysis with imputed data was 5.4% [IQR 2.4%, 9.9%] (range <0.1%-47.7%).

A further 7/159 (4%) studies in 2013 may have had imputed data, but it was not clear whether participant outcome data were available or not. In 9/91 (10%) studies using imputed data, uncertainties remained about the exact numbers of randomised participants that were included in the analysis with imputed data. In those 16 studies the median percentage of participants where it was uncertain whether data was observed or imputed was 4.3% [IQR 1.4%, 5.9%] (range 0.1%-30.8%)

In comparison, 19/46 (41%) trials from 2018 reported including participants in the analysis using imputed data. The median percentage of participants with imputed data was 8.3% [IQR 1.0%, 20.6%] (range 0.3- 39.5%). A further 3/46 (7%) studies may have had imputed data and in 3/19 (16%) studies only partial extraction of the number of participants with imputed data was possible. For these 6 studies the median percentage of participant where it was unclear whether data was observed or imputed was 9.5% [ IQR 1.6%, 14.6%] (range 1.4-17.1).

**Reporting of Imputed values within the CONSORT**

The number of participants with imputed values for the primary outcome was reported in the results’ tables or graphs in 12/91 (13%) studies using imputation in 2013 and 4/19 (21%) in 2018. Numbers with imputed data were included in the article’s text in 35/91 (38%) of studies in 2013 and 8/19 (42%) in 2018. However, in 52/91 (57%) studies in 2013 and 3/19 (16%) in 2018, the article text gave partial information, such as confirming imputation had been used without reporting for how many participants this applied, or reported some cases where imputed data was used but not all of the cases we identified.

In order to identify imputed data within the CONSORT alone, it was important that publications reported the number analysed within the diagram itself. However, only 64/91 (70%) studies using imputed data in 2013 and 14/19 (74%) studies in 2018 included the number analysed in the CONSORT. In 2013, 9/64 (14%) of studies explicitly reported the number of participants with imputed outcomes alongside the number analysed in the CONSORT diagram. (Table 3). Footnotes to the CONSORT diagram were used to provide this information in a further three studies in the 2013 cohort and one study from 2018. In addition, one study which did not report the number of participants analysed in the CONSORT diagram did report the number of imputed values within a footnote.

Imputed values could be identified through the CONSORT in 31/55 (56%) of studies in 2013 and 9/14 (64%) in 2018 where it was not explicitly reported.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **No of trials (%)** | | | | | |
| **Reporting of imputed primary outcome within the manuscript** | **2013 cohort (n=91)** | | | **2018 Cohort (n=19)** | | |
| **Yes** | **No** | **Partial** | **Yes** | **No** | **Partial** |
| Does the primary outcome results table/ graph show numbers of imputed values? | 12 (13) | 74 (81) | 5(5) | 4 (21) | 14 (74) | 1 (5) |
| Does the manuscript text report imputed values? | 35 (38) | 4 (4) | 52 (57) | 8 (42) | 8 (42) | 3 (16) |
|  | **No of trials (%)** | | | | | |
|  | **2013 cohort (n=64)a** | | | **2018 Cohort (n=14)b** | | |
| **CONSORT reporting of imputed primary outcome data** | Yes | No | Unclear | Yes | No | Unclear |
| 1. Does the CONSORT report the numbers imputed or available primary outcome data below the number analysed? | 9 (14) | 53 (83)$ | 2 (3) | - | 13 (93)$ | 1 (7) |
| 1a. If no or unclear can the reader understand it through the rest of the CONSORT diagram? (n=55)/ (n=14) | 31 (56) | 17 (31) | 7(13) | 9 (64) | 3 (21) | 2 (14) |
| 1b. If no or unclear can the reader understand it using the text to interpret the CONSORT (n=55)/ (n=14) | 25 (45) | 26 (47) | 4 (7) | 8 (57) | 6 (43) | - |

***Table 3: Reporting of imputed primary outcome data***

*Notes:* **a** *Of the 91 trials imputing data 1 had no consort and 26 did not report the number analysed* **b** *In 2018 of the 19 studies reporting imputation 5 did not report the number analysed in the CONSORT. .$3/53 in 2013 and 1/18 in 2018 did make an explicit statement about available or imputed data in the flow diagram notes.*

## Discussion:

This study examined reporting of imputed data for the primary outcome. Analysis of two cohorts of RCTs published in four major medical journals in 2013 and 2018 highlights the continued challenges of identifying whether data were observed and recorded or imputed for primary outcome analyses. There was a lack of clear information in CONSORT flow diagrams and results’ tables meaning extensive cross-checking of the entire article, including any supplementary material, is often needed to assess levels and reasons for imputation. With relatively little improvement in reporting between the two cohorts, it is recommended that the CONSORT guidelines are updated to include these details. Levels of imputed primary outcome data along with associated reasons should be explicitly reported alongside the number analysed (as is currently the case for participant exclusions).

Reporting of key elements in the CONSORT flow diagram was relatively high in both cohorts of RCTs. Compliance ranged from 67 to 100%, with the exception of reporting treatment completion and follow up, and marginally increased between 2013 and 2018. Whilst all reports included the number of randomised participants, only 76% in 2013 and 85% in 2018 included the number analysed and, in 10% of 2013 studies, this figure was not consistent with the primary outcome results’ tables. Extraction of the levels of imputed primary outcome data from the CONSORT flow diagrams requires knowledge of the numbers randomised and analysed and failure to include this crucial information impeded our data extraction.

Identification of imputed primary outcome data is intended to be understood through the reporting of ‘participant losses’ within the CONSORT flow diagram. However, the number completing follow up was only reported in 62% of 2013 studies and 68% from 2018. Even when ‘losses’ were reported within the CONSORT flow diagram, identification of participants with imputed data remained difficult. Several trials excluded some randomised participants from the analysis population whilst also including others by using imputed data. Information from the article’s text was frequently needed to understand how the reported losses had been handled in the analysis. In addition, inconsistencies were identified with some CONSORT flow diagrams reporting that participant losses were included in the analysis population with imputed values, whilst in the results they appeared to have been excluded and vice versa.

Further problems exist because studies were not clear about the relationship between treatment discontinuation and follow up.[22](#_ENREF_22) Whilst these should be reported separately to losses to follow up, several CONSORT flow diagrams reported these together, leaving the reader unclear whether ‘discontinuations’ or ‘withdrawals’ related to treatment, follow up or both.

However, identification of imputed values was largely impacted by authors’ interpretation of the requirement to report ‘participant losses’. Many CONSORT flow diagrams reported participation status at the relevant time points, which does not necessarily equate to availability of outcome data.[18](#_ENREF_18) Participants may cease participation in a RCT but still have achieved an endpoint beforehand and had this recorded, outcomes may continue to be collected from electronic health records and retained participants may fail to provide outcome data. One area where this was especially difficult were participant deaths. Primary outcome descriptions needed careful examination to establish any inclusion of all-cause or cause-specific mortality either explicitly or as part of an assessment scale (such as the five-point Glasgow Outcome Scale where brain injury patients who have died are given a score of 1). For specific-cause mortality outcomes, a breakdown of causes of death was not always reported.

All the challenges noted above were exacerbated when CONSORT flow diagrams were poorly constructed or tried to communicate information on more than one analysis populations or follow up time-point. Poor reporting meant that imputed data were often identified from only one element of the article or by piecing together partial information, leaving concerns of accuracy over incorrect interpretation by the reader or lack of full disclosure by authors. Verification of imputed data reported in the CONSORT flow diagram was not always possible because 81% of primary outcome results’ tables in 2013 and 74% in 2018 failed to include information on available outcome data and several failed to even include analysis denominators. Whilst some studies using time to event analysis explicitly reported censoring due to non-events in the CONSORT flow diagram, none reported this in the survival graphs and some did not even include numbers ‘at risk’.

Despite many reviewers evaluating missing data in trial reports either to understand the extent of the problem or for bias assessment in systematic reviews, few have discussed the problems with reporting of imputed data. Recently, Akl et al[22](#_ENREF_22) highlighted three challenges of identifying missing data similar to those outlined here: reporting of losses rather than available outcome data; reporting missing data by participant rather than outcome; and uncertainty whether participant data was imputed or excluded. Similarly, Hussain et al[14](#_ENREF_14) noted the problems associated with the ambiguous terminology of ‘withdrawal’ and ‘loss to follow’, which also fails to report the true nature of the losses. Consequently, it is becoming apparent that missing outcome data may be substantially underestimated within RCTs[23](#_ENREF_23) with important implications for their findings and systematic reviews[22](#_ENREF_22).

As statisticians are encouraged to use imputation in the primary trial analysis, rather than a complete case analysis[8](#_ENREF_8) it is important that the challenges of reporting imputed data are addressed. As there was little improvement in reporting between the two cohorts over five years, we recommend further refinement of the CONSORT guidance if readers are to be able to reliably assess levels and causes of imputed primary outcome data. The number of participants included in the analysis with imputed data along with reasons should be explicitly reported within the manuscript, along with the number analysed in the CONSORT flow diagram in line with guidance for exclusions. Results’ tables should include information on the number of participants with imputed data at each time point in the analysis. Where this is not feasible, or missing data are complex, additional information should be included in the supplementary material. Importantly, this new guidance should also apply to analysis methods considered to account for missing data, such as survival analysis, where the use of extended risk tables would be beneficial[24](#_ENREF_24).

**Limitations**

Extraction of imputed data was difficult for this study and authors were not contacted to verify the accuracy so the levels of imputed data within the cohort should be taken with caution. Due to the time-consuming nature of data extraction, we opted to assess papers from the first quarter of 2018 only, thus the cohort was relatively small for analysis. However, it broadly supports the issues identified in the 2013 cohort.

Data used in this analysis were originally collected for a study designed to assess the levels and reported reasons for missing data. Assumptions were used to aid data extraction in areas known to be problematic, such as the ambiguous reporting of ‘withdrawal’. Consequently, the levels of uncertainty around availability of primary outcome data may be underestimated. The reliance on published reports of RCTs in four major medical journals means that the scale of these problems for other journals is unknown

## Conclusion:

The number of participants included in the primary outcome analysis using imputed rather than observed values is not easily identified from the CONSORT flow diagram and is infrequently reported within results’ tables. CONSORT flow diagrams often report participation status at relevant time points but this does not necessarily correlate to availability of primary outcome data. Authors should be mindful of the issues we have highlighted and seek to improve clarity of reporting imputed values. We recommend changes to the CONSORT guidelines to encourage explicit reporting of imputed values against the analysis population so that readers are able to assess the reliability of trial findings.

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## References:

1. Newell DJ. Intention-to-Treat Analysis: Implications for Quantitative and Qualitative Research. *International Journal of Epidemiology* 1992; 21: 837-841. DOI: 10.1093/ije/21.5.837.

2. Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011; 2: 109-112. DOI: 10.4103/2229-3485.83221.

3. McCoy CE. Understanding the Intention-to-treat Principle in Randomized Controlled Trials. *West J Emerg Med* 2017; 18: 1075-1078. 09/18. DOI: 10.5811/westjem.2017.8.35985.

4. Altman DG. Missing outcomes in randomized trials: addressing the dilemma. *Open medicine : a peer-reviewed, independent, open-access journal* 2009; 3: e51-53. 2009/12/01.

5. Hollis S and Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *Bmj* 1999; 319: 670-674.

6. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* 2009; 338.

7. Akl EA, Shawwa K, Kahale LA, et al. Reporting missing participant data in randomised trials: systematic survey of the methodological literature and a proposed guide. 2015.

8. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *Bmj* 2009; 338: b2393. 2009/07/01. DOI: 10.1136/bmj.b2393.

9. Jakobsen JC, Gluud C, Wetterslev J, et al. When and how should multiple imputation be used for handling missing data in randomised clinical trials - a practical guide with flowcharts. *BMC Med Res Methodol* 2017; 17: 162. 2017/12/07. DOI: 10.1186/s12874-017-0442-1.

10. Bell ML, Fiero M, Horton NJ, et al. Handling missing data in RCTs; a review of the top medical journals. *BMC Med Res Methodol* 2014; 14: 118. 2014/11/20. DOI: 10.1186/1471-2288-14-118.

11. Schulz KF, Altman DG, Moher D, et al. Consort 2010 statement: Updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine* 2010; 152: 726-732. DOI: 10.7326/0003-4819-152-11-201006010-00232.

12. Toerien M, Brookes ST, Metcalfe C, et al. A review of reporting of participant recruitment and retention in RCTs in six major journals. *Trials* 2009; 10: 52. 2009/07/14. DOI: 10.1186/1745-6215-10-52.

13. Walters SJ, Bonacho dos Anjos Henriques-Cadby I, Bortolami O, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. *BMJ Open* 2017; 7. 10.1136/bmjopen-2016-015276.

14. Hussain JA, Bland M, Langan D, et al. Quality of missing data reporting and handling in palliative care trials demonstrates that further development of the CONSORT statement is required: a systematic review. *Journal of Clinical Epidemiology* 2017. DOI: <http://dx.doi.org/10.1016/j.jclinepi.2017.05.009>.

15. Powney M, Williamson P, Kirkham J, et al. A review of the handling of missing longitudinal outcome data in clinical trials. *Trials* 2014; 15: 237. 2014/06/21. DOI: 10.1186/1745-6215-15-237.

16. Rombach I, Knight R, Peckham N, et al. Current practice in analysing and reporting binary outcome data-a review of randomised controlled trial reports. *BMC Med* 2020; 18: 147. 2020/06/09. DOI: 10.1186/s12916-020-01598-7.

17. Lieber R, Pandis N and Faggion CM, Jr. Reporting and handling of incomplete outcome data in implant dentistry: A survey of randomized clinical trials. *J Clin Periodontol* 2020; 47: 257-266. 2019/11/21. DOI: 10.1111/jcpe.13222.

18. Mackinnon A. The use and reporting of multiple imputation in medical research – a review. *Journal of Internal Medicine* 2010; 268: 586-593. DOI: 10.1111/j.1365-2796.2010.02274.x.

19. Hayati Rezvan P, Lee KJ and Simpson JA. The rise of multiple imputation: a review of the reporting and implementation of the method in medical research. *BMC Medical Research Methodology* 2015; 15: 30. DOI: 10.1186/s12874-015-0022-1.

20. Wood AM, White IR and Thompson SG. Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals. *Clinical trials* 2004; 1: 368-376. DOI: 10.1191/1740774504cn032oa.

21. Higgins J and Green Se. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. ed. Available from <www.handbook.cochrane.org>. : The Cochrane Collaboration, 2011.

22. Akl EA, Kahale LA, Ebrahim S, et al. Three challenges described for identifying participants with missing data in trials reports, and potential solutions suggested to systematic reviewers. *Journal of Clinical Epidemiology* 2016; 76: 147-154. Article. DOI: 10.1016/j.jclinepi.2016.02.022.

23. Kahale LA, Diab B, Khamis AM, et al. Potentially missing data are considerably more frequent than definitely missing data: a methodological survey of 638 randomized controlled trials. *Journal of Clinical Epidemiology* 2019; 106: 18-31. Review Article. DOI: 10.1016/j.jclinepi.2018.10.001.

24. Morris TP, Jarvis CI, Cragg W, et al. Proposals on Kaplan–Meier plots in medical research and a survey of stakeholder views: KMunicate. *BMJ Open* 2019; 9.