St. Joseph's Healthcare Hamilton

McMaster University
HEALTH RESEARCH METHODS, EVIDENCE, AND IMPACT

The Research Institute of St. Joe's Hamilton

So, what if I have some missing data or patients in my clinical trial: what's the big deal, and wouldn't imputation solve the problem?

Lehana Thabane

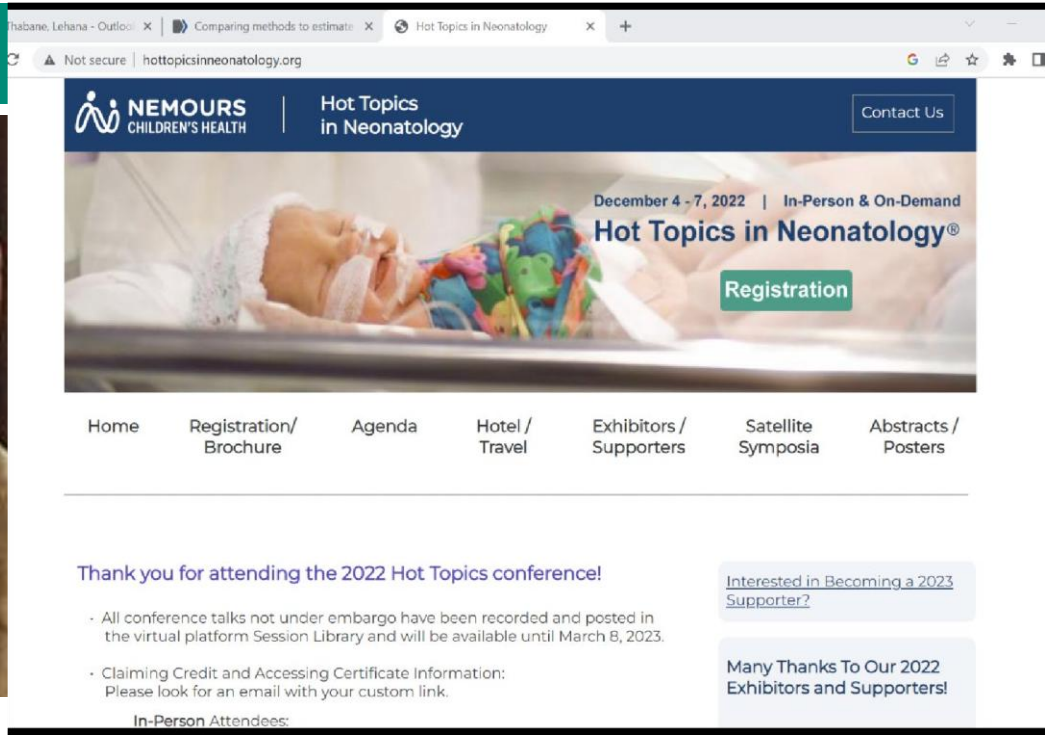
Disclosure and COI

- No financial COI to declare

- As a professor, I get academic credit by giving presentations like this

I recently presented a version of this talk at the meeting on Hot Topics in Neonatology in Washington DC in 2022

Barbara Schmidt and Haresh Kirpalani



Missing Outcome Data in Recent Perinatal and Neonatal Clinical Trials

Missing outcome data in clinical trials may jeopardize the validity of the trial results and inferences for clinical practice. Although sick and preterm newborns are treated as a captive patient population during their stay in the NICUs, their long-term outcomes are often ascertained after discharge. This greatly increases the risk of attrition. We surveyed recently published perinatal and neonatal randomized trials in 7 high-impact general medical and pediatric journals to review the handling of missing primary outcome data and any choice of imputation methods. Of 87 eligible trials in this survey, 77 (89%) had incomplete primary outcome data. The missing outcome data were not discussed at all in 9 reports (12%). Most study teams restricted their main analysis to participants with complete information for the primary outcome (61 trials; 79%). Only 38 of the 77 teams (49%) performed sensitivity analyses using a variety of imputation methods. We conclude that the handling of missing primary outcome data was frequently inadequate in recent randomized perinatal and neonatal trials. To improve future approaches to missing outcome data, we discuss the strengths and limitations of different imputation methods, the appropriate estimation of sample size, and how to deal with data withdrawal. However, the best strategy to reduce bias from missing outcome data in perinatal and neonatal trials remains prevention. Investigators should anticipate and preempt missing data through careful study design, and closely monitor all incoming primary outcome data for completeness during the conduct of the trial.

SPECIAL ARTICLE

Making the Most of Missing Data

Clinical trials are demanding, resource intensive, and essential to the health and well-being of children. In this issue of *Pediatrics*, Li and colleagues[1] outline the magnitude of an often-overlooked problem within neonatal and perinatal clinical trials. Their results demonstrate that missing primary outcome data are often ignored or mishandled, which decreases statistical power, increases bias, and may jeopardize the validity of clinical trial results. The authors provide practical approaches to avoid missing outcome data through clinical trial design strategies and review sensitivity analyses and imputation methods to mitigate the risk of bias.

COMMENTARY

research.stjoes.ca

How prevalent is problem of missing data in perinatal and neonatal trials?

- We searched Medline (via PubMed) for RCTs that enrolled newborns or their birthing parents, reported outcomes n the children
- Trials published between January 1, 2020, and December 31, 2022.
- Sources:
  - ✓ High-impact general medical journals: Lancet, NEJM, JAMA, BMJ

- ✓ Pediatric specialty journals: JAMA Pediatrics, Pediatrics, Lancet Child and Adolescent Health.

Setting the stage

- ❑ We are talking about missing outcome data in a trial
  - ✓ Part or all outcome data for some patients
  - ✓ These are not missing by design

- We are NOT talking about missing demographic or prognostic data
- This assumes that we have information on some or all baseline characteristics

TABLE 1 Practice of Handling Missing Primary Outcome Data in 77 Perinatal and Neonatal RCTs Published Between 2020 and 2022 in 7 High-Profile Pediatric and General Journals

Practice of Handling Missing Outcome Data	Total Number of RCTs ($N = 77$), No. (%)	RCTs in Pediatric Journals ($N = 35$), No. (%)	RCTs in General Journals ($N = 42$), No. (%)	*P*
Not reporting missing data in the results	9 (12)	7 (20)	2 (5)	.07[d]
Primary approach for intervention effect estimates				
Complete-case analysis	61 (79)	23 (66)	38 (91)	<.01[d]
Best-case scenario	1 (1)	0	1 (2)	
Unclear	15 (20)	12 (34)	3 (7)	
Sensitivity analysis performed for intervention effect estimates				
Yes	38 (49)	10 (29)	28 (67)	<.01[e]
No	39 (51)	25 (71)	14 (33)	
Imputation methods used in 38 RCTs with sensitivity analysis[a]				
Single imputation[b]	15 (40)	2 (20)	13 (46)	.26[d]
Multiple imputation	22 (58)	4 (40)	18 (64)	.27[d]
Inverse probability weighting method	3 (8)	2 (20)	1 (4)	.16[d]
Model-based imputation[c]	2 (5)	0	2 (7)	—
Unclear	3 (8)	2 (20)	1 (4)	.16[d]
Sensitivity analysis yields different results from primary approach				
Yes	1 (3)	0	1 (4)	.74[d]
No	31 (81)	8 (80)	23 (82)	
Unclear	6 (16)	2 (20)	4 (14)	

JAMA Pediatrics, *Pediatrics*, and *Lancet Child and Adolescent Health*; *Lancet*, *New England Journal of Medicine*, *Journal of the American Medical Association*, and *British Medical Journal*. —, no comparison was made.

[a] RCTs do not add up to 38 because some trials used >1 imputation method.

[b] The following single imputation methods were used: Worst/best-case scenario (11 RCTs; 73%), mean/mode imputation (3 RCTs; 20%), and last observation carried forward (1 RCT; 7%).

[c] The following model-based imputation methods were used: Linear mixed-effects model and pattern-mixture model (1 RCT or 50% for each method).

[d] Calculated from Fisher's exact test.

[e] Calculated from χ^2 test.

What did we find?

- Included 87 eligible perinatal and neonatal RCTs
- 77/87 (89%) trials had missing primary outcome data
- 61 (79%) used a complete-case analysis as their primary approach

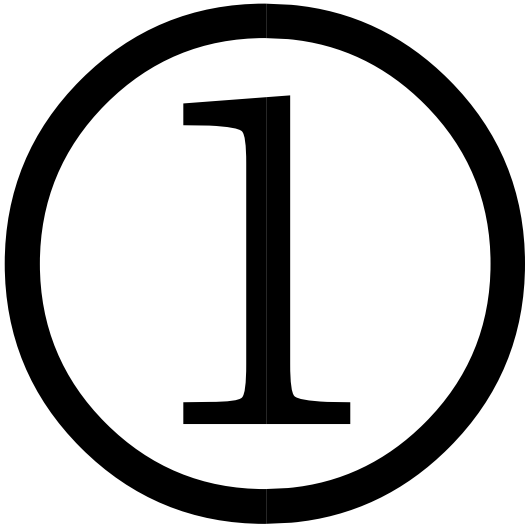
- 38 (49%) trial reports included some sensitivity analysis using a variety of imputation methods

- There is high prevalence of missing data in recent perinatal and neonatal trials
- The handling of missing primary outcome data has been largely inadequate in recent perinatal and neonatal trials

Unfortunately, perinatal and neonatal area **is not** the only clinical area challenged by these deficiencies

This talk was about imputation of missing data in trials: What you need to know about what imputation is, why it is necessary, what the current practice looks like, what the best

methods to impute are, what it cannot do, and how to prevent the need for it


1

What is imputation of missing data?

What does imputation mean?

"The practice of filling in missing data with plausible values."

(Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8:3–15)

In general, imputation methods fall under 4 main categories

- Single imputation methods: replacing missing data with single plausible value
  - ✓ Mean/median imputation
  - ✓ Last observation carried forward/backward
  - ✓ Worst/best case scenario
  - ✓ Prediction of missing data

- Multiple imputation methods: replacing missing data with multiple plausible values
- Model-based imputation methods
  - ✓ Likelihood based methods
  - ✓ Mixture models
  - ✓ Monte Carlo Markov Chain (MCMC)
  - ✓ EM algorithm
  - ✓ AI methods
- Weighting methods
  - ✓ Inverse probability weighting

Complete Case Analysis

Time 1: no missing data **Time 2: with missing data**

Analysis Result Using Complete Cases

Single Imputation Analysis

Time 1: no missing data

Time 2: with missing data

Analysis based on imputed dataset

Adhoc: Single Imputation Analysis

Time 1: no missing data

Time 2: with missing data

Multiple Imputation Analysis

The steps for model-based imputation

1. Use ML (maximum likelihood) to estimate parameters based on complete data
2. Use ML to impute missing data based on estimated parameters in Step 1
3. Re-do step 1 based on imputed dataset

4. Repeat Steps 1-3 until no changes in parameter estimates

Inverse Probability Weighting Method

- **Inverse probability weighting** in conjunction with regression modeling
- Also commonly referred to as
  - ✓ *weighted complete-case analysis*
  - ✓ *inverse probability of participation/attrition weighting*

- The IPW is based on the assumption that individual information that **can predict the probability of inclusion (non-missingness) are available**
- The procedure is done in the following steps:
  1. Calculate the **probability of non-missing information PS(X)** using a logistic regression model—the response is the nonmissingness and the covariates are its possible predictors.
  2. The weight of each subject is given by the inverse of the predicted probability (ie. ***weight = 1/PS(X)***)

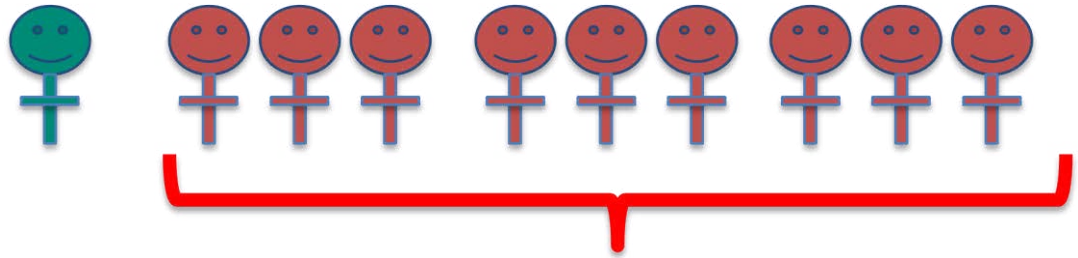
3. Then the analysis is performed using a **weighted regression model**

Inverse PSW Method

Probability score PS(X) = 0.10

IPW= 1 = 10

0.10



IPW is used to **inflate** the weight for participants who

are under-represented due to missing data from similar participants

- There are several methods for dealing with missing data

- All can be classified under 4 classes: single, multiple, model-based imputation and weighting

Why do we need imputation for missing data?

In general, missing data create many problems including

- ❑ Increase the risk of bias
- ❑ Decrease statistical power
- ❑ Reduce the representativeness of the sample

- Negatively impact the
  - ✓applicability of results
  - ✓reliability of results
  - ✓interpretability of results
  - ✓validity of the statistical methods (at least in trials)

So, imputation for missing data is a viable solution to these problems!

In practice, evaluation of the quality or certainty evidence from published study reports require that

we assess the risk of bias in the evidence

The Cochrane Risk of Bias Tool

2 (RoB 2) and the ROBINS-1 for assessment of risk in observational studies tool partly

require evaluation of the risk of bias due to missing data

1. bias arising from the randomization process:

2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome; and
5. bias in selection of the reported result.

ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions

Jonathan AC Sterne,[1] Miguel A Hernán,[2] Barnaby C Reeves,[3] Jelena Savović,[1,4] Nancy D Berkman,[5] Meera Viswanathan,[6] David Henry,[7] Douglas G Altman,[8] Mohammed T Ansari,[9] Isabelle Boutron,[10] James R Carpenter,[11] An-Wen Chan,[12] Rachel Churchill,[13] Jonathan J Deeks,[14] Asbjørn Hróbjartsson,[15] Jamie Kirkham,[16] Peter Jüni,[17] Yoon K Loke,[18] Theresa D Pigott,[19] Craig R Ramsay,[20] Deborah Regidor,[21] Hannah R Rothstein,[22] Lakhbir Sandhu,[23] Pasqualina L Santaguida,[24] Holger J Schünemann,[25] Beverly Shea,[26] Ian Shrier,[27] Peter Tugwell,[28] Lucy Turner,[29] Jeffrey C Valentine,[30] Hugh Waddington,[31] Elizabeth Waters,[32] George A Wells,[33] Penny F Whiting,[34] Julian PT Higgins[35]

Cite this as: *BMJ* 2016;355:i4919
http://dx.doi.org/10.1136/bmj.i4919

Table 1 | Bias domains included in ROBINS-I

Domain	Explanation
Pre-intervention	**Risk of bias assessment is mainly distinct from assessments of randomised trials**
Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline
Bias in selection of participants into the study	When exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical This form of selection bias is distinct from confounding—A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention
At intervention	**Risk of bias assessment is mainly distinct from assessments of randomised trials**
Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias
Post-intervention	**Risk of bias assessment has substantial overlap with assessments of randomised trials**
Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s) Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention)
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (such as differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as confounders
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention status, if different methods are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings and prevents the estimate from being included in a meta-analysis (or other synthesis)

Therefore, it is required in the overall evaluation of the certainty of evidence through GRADE

Mac GRADE Centre | McMaster University

As a result…

Reporting guidelines for study protocols recommend description

of how missing data will be handled

SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials

An-Wen Chan,[1] Jennifer M Tetzlaff,[2] Peter C Gøtzsche,[3] Douglas G Altman,[4] Howard Mann,[5] Jesse A Berlin,[6] Kay Dickersin,[7] Asbjørn Hróbjartsson,[3] Kenneth F Schulz,[8] Wendy R Parulekar,[9] Karmela Krleža-Jeric,[10] Andreas Laupacis,[11] David Moher[2 10]

Guideline	Item
SPIRIT (BMJ. 2013;346:e7586.)	20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
SPIRIT-PRO (JAMA. 2018;319(5):483494)	20c State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).

SPIRIT-AI (BMJ 2020;370:m3210)	20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)
SPENT 2019 (BMJ 2020;368:m122)	20c Statistical methods to handle missing data (eg, imputation). In addition for series: Definition of analysis population relating to protocol nonadherence (eg, as-randomised analysis).

The SAP guideline for RCTs recommends it

Clinical Review & Education

JAMA | Special Communication

JAMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD; Ashma Krishan, BSc; Deborah Stocken, PhD; Steff Lewis, PhD; Edmund Juszczak, MSc; Caroline Doré, BSc; Paula R. Williamson, PhD; Douglas G. Altman, DSc; Alan Montgomery, PhD; Pilar Lim, PhD; Jesse Berlin, ScD; Stephen Senn, PhD; Simon Day, PhD; Yolanda Barbachano, PhD; Elizabeth Loder, MD, MPH

Item 28: Missing Data

Reporting and assumptions/statistical methods to handle missing data (eg, multiple imputation)

It never used to be explicitly stated in the CONSORT

Statement and its extensions

CONSORT 2025 statement: updated guideline for reporting randomised trials

Sally Hopewell*, An-Wen Chan, Gary S Collins, Asbjørn Hróbjartsson, David Moher, Kenneth F Schulz, Ruth Tunn, Rakesh Aggarwal, Michael Berkwits, Jesse A Berlin, Nita Bhandari, Nancy J Butcher, Marion K Campbell, Runcie C W Chidebe, Diana Elbourne, Andrew Farmer, Dean A Fergusson, Robert M Golub, Steven N Goodman, Tammy C Hoffmann, John P A Ioannidis, Brennan C Kahan, Rachel L Knowles, Sarah E Lamb, Steff Lewis, Elizabeth Loder, Martin Offringa, Philippe Ravaud, Dawn P Richards, Frank W Rockhold, David L Schriger, Nandi L Siegfried, Sophie Staniszewska, Rod S Taylor, Lehana Thabane, David Torgerson, Sunita Vohra, Ian R White, Isabelle Boutron

Well designed and properly executed randomised trials are considered the most reliable evidence on the benefits of healthcare interventions. However, there is overwhelming evidence that the quality of reporting is not optimal. The CONSORT (Consolidated Standards of Reporting Trials) statement was designed to improve the quality of reporting and provides a minimum set of items to be included in a report of a randomised trial. CONSORT was first published in 1996, then updated in 2001 and 2010. Here, we present the updated CONSORT 2025 statement, which aims to account for recent methodological advancements and feedback from end users. We conducted a scoping review of the literature and developed a project-specific database of empirical and theoretical evidence related to CONSORT, to generate a list of potential changes to the checklist. The list was enriched with recommendations provided by the lead authors of existing CONSORT extensions (Harms, Outcomes, Non-pharmacological Treatment), other related reporting guidelines (TIDieR) and recommendations from other sources (eg, personal communications). The list of potential changes to the checklist was assessed in a large, international, online, three-round Delphi survey involving 317 participants and discussed at a two-day online expert consensus meeting of 30 invited international experts. We have made substantive changes to the CONSORT checklist. We added seven new checklist items, revised three items, deleted one item, and integrated several items from key CONSORT extensions. We also restructured the CONSORT checklist, with a new section on open science. The CONSORT 2025 statement consists of a 30-item checklist of essential items that should be included when reporting the results of a randomised trial and a diagram for documenting the flow of participants through the trial. To facilitate implementation of CONSORT 2025, we have also developed an expanded version of the CONSORT 2025 checklist, with bullet points eliciting critical elements of each item. Authors, editors, reviewers, and other potential users should use CONSORT 2025 when writing and evaluating manuscripts of randomised trials to ensure that trial reports are clear and transparent.

Published Online April 14, 2025 https://doi.org/10.1016/S0140-6736(25)00672-5

Oxford Clinical Trials Research Unit, Centre for Statistics in Medicine, University of Oxford, Oxford UK (Prof S Hopewell DPhil, R Tunn DPhil); Department of Medicine, Women's College Research Institute, University of Toronto, Toronto, ON, Canada (Prof A-W Chan MD DPhil); UK EQUATOR Centre, Centre for Statistics in Medicine, University of Oxford, Oxford, UK (Prof G S Collins PhD); Centre for Evidence-Based Medicine Odense and Cochrane Denmark, Department of Clinical Research, University of Southern Denmark, Odense, Denmark (Prof A Hróbjartsson PhD); Open

	Number	CONSORT 2025 checklist item description
(Continued from previous page)		
Randomisation		
Sequence generation	17a	Who generated the random allocation sequence and the method used
	17b	Type of randomisation and details of any restriction (eg, stratification, blocking and block size)
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (eg, central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence
Blinding	20a	Who was blinded after assignment to interventions (eg, participants, care providers, outcome assessors, data analysts)
	20b	If blinded, how blinding was achieved and description of the similarity of interventions
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms
	21b	Definition of who is included in each analysis (eg, all randomised participants), and in which group
	21c	How missing data were handled in the analysis
	21d	Methods for any additional analyses (eg, subgroup and sensitivity analyses), distinguishing prespecified from post hoc

The Research In of St

Not it is! Fresh from the press today!

research.stjoes.ca

SPIRIT

CONSORT

Enhancing the transparency and reporting of randomised trials: update of the SPIRIT 2013 and CONSORT 2010 Statements

Virtual consensus meeting • 1st - 2nd March 2023

The Research In of St

research.stjoes.ca

Update on CONSORT 2025 FYI

- **New CONSORT 2025 Update**
  - ✓ BMJ: www.bmj.com/content/389/bmj-2024-081123
  - ✓ Lancet: www.thelancet.com/journals/lancet/article/PIIS0140-6736(25)00672-5/abstract
  - ✓ JAMA: https://jamanetwork.com/journals/jama/fullarticle/2832868
  - ✓ Nature Medicine: www.nature.com/articles/s41591-025-03635-5
  - ✓ PLoS Medicine: https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1004587
- **New CONSORT 2025 E&E**
  - ✓ BMJ E&E: https://www.bmj.com/content/389/bmj-2024-081124

- **BMJ has also published several editorials highlighting the importance of CONSORT (and Doug Altman's legacy and pivotal role) and reporting guidelines more generally:**
  - ✓ https://www.bmj.com/content/389/bmj.r734
  - ✓ https://www.bmj.com/content/389/bmj.r718 ✓ https://www.bmj.com/content/389/bmj.r494
- **New CONSORT/SPIRIT 2025 Website**
  - ✓ www.consort-spirit.org

Update on SPIRIT 2025 FYI

- **New SPIRIT 2025 Update**
  - ✓ BMJ: https://doi.org/10.1136/bmj-2024-081477

- ✓ JAMA: https://doi.org/10.1001/jama.2025.4486
- ✓ Lancet: https://doi.org/10.1016/S0140-6736(25)00770-6
- ✓ PLOS Med: https://doi.org/10.1371/journal.pmed.1004589
- ✓ Nature Med: https://doi.org/10.1038/s41591-025-03668-w

❑ New SPIRIT 2025 E&E

- ✓ BMJ E&E: https://doi.org/10.1136/bmj-2024-081660

❑ New CONSORT/SPIRIT 2025 Website

- ✓ www.consort-spirit.org

But, it is expected that if planned in the SAP or protocol, then the results

on handling of missing data will be reported

Regulatory agencies have provided guidance on how address it in

regulatory studies

The Prevention and Treatment of Missing Data in Clinical Trials: An FDA Perspective on the Importance of Dealing With It

RT O'Neill[1] and R Temple[2]

The Research In
of St

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

2 July 2010
EMA/CPMP/EWP/1776/99 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Guideline on Missing Data in Confirmatory Clinical Trials

Discussion in the Efficacy Working Party	June 1999/ November 2000
Transmission to CPMP	January 2001
Released for consultation	January 2001
Deadline for Comments	April 2001
Discussion in the Efficacy Working Party	October 2001
Transmission to CPMP	November 2001
Adoption by CPMP	November 2001
Draft Rev. 1 Agreed by Efficacy Working Party	April 2009
Adoption by CHMP for release for consultation	23 April 2009
End of consultation (deadline for comments)	31 October 2009
Rev. 1 Agreed by Efficacy Working Party	April 2010
Adoption by CHMP	24 June 2010
Date for coming into effect	1 January 2011

This guideline replaces Points to Consider on Missing Data in Clinical Trials (CPMP/EWP/1776/99).

Keywords	*Baseline Observation Carried Forward (BOCF), Generalised Estimating Equations (GEE), Last observation carried forward (LOCF), Missing at random (MAR), Missing completely at random (MCAR), Missing Data, Mixed Models for*

September 1998
CPMP/ICH/363/96

ICH Topic E 9
Statistical Principles for Clinical Trials

Step 5

NOTE FOR GUIDANCE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS
(CPMP/ICH/363/96)

TRANSMISSION TO CPMP	February 1997
RELEASE FOR CONSULTATION	February 1997
COMMENTS REQUESTED BEFORE	June 1997
FINAL APPROVAL BY CPMP	March 1998
DATE FOR COMING INTO OPERATION	September 1998

Other major methodology groups have set standards of

how to deal with it

PCORI METHODOLOGY REPORT

October 2021

The Methodology Standards were updated in February 2019 and are available at www.pcori.org/methodology-standards.

pcori

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

The Research In
of St

4: STANDARDS FOR PREVENTING AND HANDLING MISSING DATA

MD-1: Describe methods to prevent and monitor missing data.
Investigators should explicitly state potential reasons that study data may be missing. Missing data can occur from patient dropout, nonresponse, data collection problems, incomplete data sources, and/or administrative issues. As relevant, the protocol should include the anticipated amount of and reasons for missing data, plans to prevent missing data, and plans to follow up with study participants. The study protocol should contain a section that addresses steps taken in study design and conduct to monitor and limit the impact of missing data. This standard applies to all study designs for any type of research question.

MD-2: Use valid statistical methods to deal with missing data that properly account for statistical uncertainty owing to missingness.
Valid statistical methods for handling missing data should be prespecified in study protocols. The analysis should explore the reasons for missing data and assess the plausibility of the assumptions associated with the statistical methods. The potential impact of missing data on the results and limitations of the approaches used to handle the missing data should be discussed.

Estimates of treatment effects or measures of association should be based on statistical inference procedures that account for statistical uncertainty attributable to missing data. Methods used for imputing missing data should produce valid confidence intervals and permit unbiased inferences based on statistical hypothesis tests. Bayesian methods, multiple imputation, and various likelihood-based methods are valid statistical methods for dealing with missing data. Single imputation methods, such as last observation carried forward, baseline observation carried forward, and mean value imputation, are discouraged as the primary approach for handling missing data in the analysis. If single imputation–based methods are used, investigators must provide a compelling scientific rationale for why the method is appropriate. This standard applies to all study designs for any type of research question.

MD-3: Record and report all reasons for dropout and missing data, and account for all patients in reports.
Whenever a participant drops out of a research study, the investigator should document the following: (1) the specific reason for dropout, in as much detail as possible; (2) who decided that the participant would drop out; and (3) whether the dropout involves participation in all or only some study activities. Investigators should attempt to continue to collect information on key outcomes for participants unless consent is withdrawn. All participants included in the study should be accounted for in study reports, regardless of whether they are included in the analyses. Any planned reasons for excluding participants from analyses should be described and justified. In addition, missing data owing to other mechanisms (e.g., nonresponse and data entry/collection) should be documented and addressed in the analyses.

MD-4: Examine sensitivity of inferences to missing data methods and assumptions, and incorporate it into the interpretation.
Examining sensitivity to the assumptions about the missing data mechanism (i.e., sensitivity analysis) should be a mandatory component of the study protocol, analysis, and reporting. This standard applies to all study designs for any type of research question. Statistical summaries should be used to describe missing data in studies, including a comparison of baseline characteristics of units (e.g., patients, questions, clinics) with and without missing data. These quantitative results should be incorporated into the interpretation of the study and reflected in the discussion section and, when possible, the abstract of any reports.

Rationale for These Standards
These standards apply to both missing data and inaccurate data (e.g., in electronic health records), the treatment of which are governed by similar design and analytical considerations (Benchimol et al. 2015). Missing data are unrecorded or inaccurate values or unavailable information that would be meaningful for data analysis and could affect results and conclusions. Possible reasons for missing data include the following:

- Recoding or measurement errors
- Utilizing data sets derived from records not intended for research, such as those generated from routine clinical care
- Involving or evaluating participant populations that are harder to retain over time, making it difficult to collect data


3

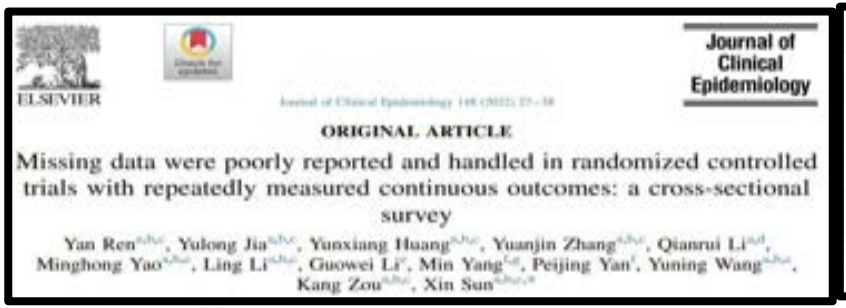
What is the current practice?

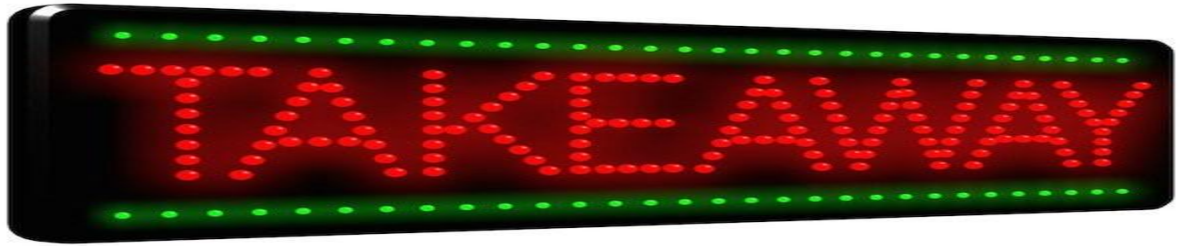
Unfortunately, the practice is

not good!

Many reviews show that the practice is **far from optimal.**

And the latest reviews show that **nothing has changed**





- **The practice is variable**

- The least optimal methods are frequently used
- The most appropriate methods are infrequently used
- Regardless of whether or not the design is a randomized or non-randomized, the handling of missing data in longitudinal studies is inadequate


4

What are the best imputation methods?

It depends!

On What?

The choice of methods depends on the

assumptions about the pattern of missingness

Different patterns of missing data

Missing completely at random (MCAR)

- The likelihood of missing data is unrelated to any observed or unobserved variables.

Missing at random (MAR)

- The likelihood of missing data is related to observed variables but not to unobserved variables

Not missing at random (NMAR)

- The likelihood of missing data depends on the unobserved data

Madison Zhang
Former PhD HRM Student

ELSEVIER

Journal of Clinical Epidemiology

A systematic survey of the methods literature on the reporting quality and optimal methods of handling participants with missing outcome data for continuous outcomes in randomized controlled trials

Yuqing Zhang[a,b], Akram Alyass[a], Thuva Vanniyasingam[a], Behnam Sadeghirad[a,c], Iván D. Flórez[a,d], Sathish Chandra Pichika[a], Sean Alexander Kennedy[e], Ulviya Abdulkarimova[f], Yuan Zhang[a], Tzvia Iljon[f], Gian Paolo Morgano[g], Luis E. Colunga Lozano[g], Fazila Abu Bakar Aloweni[h], Luciane C. Lopes[i,j], Juan José Yepes-Nuñez[a,d], Yutong Fei[k], Li Wang[l], Lara A. Kahale[m], David Meyre[a,n], Elie A. Akl[o], Lehana Thabane[a], Gordon H. Guyatt[p,a]

- Consider using multiple imputation or mixed model methods—they have been shown were superior to other methods in terms of overall performance and bias,
- Avoid LOCF approach
- Perform sensitivity analysis to assess robustness

What is performance based on?

STATISTICS IN MEDICINE
Statist. Med. 2006; **25**:4279–4292
Published online 31 August 2006 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.2673

The design of simulation studies in medical statistics

Andrea Burton[1,2,*,†], Douglas G. Altman[1], Patrick Royston[1,3] and Roger L. Holder[4]

[1]*Cancer Research UK/NHS Centre for Statistics in Medicine, Oxford, U.K.*
[2]*Cancer Research UK Clinical Trials Unit, University of Birmingham, Birmingham, U.K.*
[3]*MRC Clinical Trials Unit, London, U.K.*
[4]*Department of Primary Care and General Practice, University of Birmingham, Birmingham, U.K.*

of St

Bias: deviation from the truth (ie. Specified effect value)

Accuracy: mean square error (MSE), which incorporates both bias and variability of the effect

Coverage: the proportion of times that the obtained confidence interval contains the true specified effect value

Empirical Type I error rate: the proportion of simulation samples in which the null hypothesis of no effect is rejected at the nominal, usually 5 per cent, significance level, when the null hypothesis is false

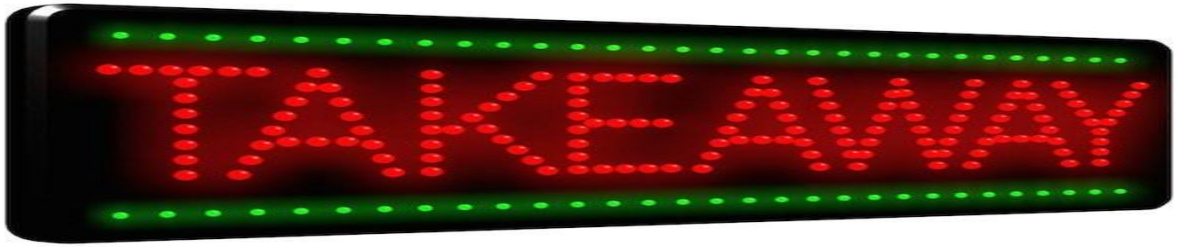
Empirical type II error rate: the proportion of *p*-values from testing the null hypothesis of no difference on each simulated sample that are less than the nominal 5 per cent significance level, when the null hypothesis is true

Empirical Power: 1- Type II error rate

Important

Please note that ignoring missing data is essentially another way of handling missing data which

assumes that they are missing completely at random



- The choice of method is dependent on assumptions on pattern of missingness
- In general,
  - ✓ single imputation methods such LOCF, mean imputation, worst/best case scenarios, don't perform well
  - ✓ MI or model-based imputation methods perform better


5

What imputation cannot do

Imputed data cannot…

- be used as replacement for better design and conduct of trials to prevent missing data!

- tell why data were missing!
- tell whether or not the imputed value is true
- be used as clinical decisions for individual patients with missing data!

I tell colleagues that the best approach to missing data is to PREVENT IT!

Published in final edited form as:
Ann Intern Med. 2011 January 18; 154(2): 113–117. doi:10.1059/0003-4819-154-2-201101180-00010.

Addressing Missing Data in Clinical Trials

Thomas R. Fleming, PhD
University of Washington, Seattle, Washington

Tom Fleming

"The preferred and often only satisfactory approach to addressing missing data is to prevent it"

Strategies for preventing attrition

(DeMauro SE. Does Attrition Still Matter And How Can It Be Reduced? Hot Topics in Neonatology. Washington DC, 2022)

- ✓ Engage families in the design of your study
- ✓ Employ peer navigators to support study participants
- ✓ Help families travel or travel to the family/school
- ✓ Have flexible hours and scheduling
- ✓ Provide childcare for siblings
- ✓ Develop and use remote/virtual assessments
- ✓ Make the assessments relevant (ie patient centered)

- ✓ Keep in touch, remind them that their contributions are valued

Sara B. DeMauro, MD, MSCE, is an Associate Professor of Pediatrics at the University of Pennsylvania Perelman School of Medicine

There is some hope that decentralizing clinical

trials will also reduce the likelihood of missing data!

My advice: Use practical commonsense measures

Work with mentors who are experienced in running trials or

Collaborate with a biostatistician or methodologist

Invest in hiring qualified research staff (research coordinator)

Communicate with and educate patients about the trial/study and importance of complete data for study integrity

Set targets for missing data and devise strategies if not Allocate resources to effective data collection, and following up patients for

Plan sensitivity analyses to assess the impact of missingness on key findings using best methods depending on the nature of missingness

Follow proper reporting guidance on what and how to report

Design a simple, easy-toimplement protocol with objectives in mind, with lots of flexibility to minimize attrition

There is another rare, but generally unrecognized

problem that can lead to missing data in trials

Patients requesting withdrawal of their already collected data at the time when they withdraw from a study

Contemporary Clinical Trials 32 (2011) 318–322

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Editorial letter

Data withdrawal in randomized controlled trials: Defining the problem and proposing solutions
A commentary

Chenglin Ye [a,d,e], Lora Giangregorio [b], Anne Holbrook [c,d,f], Eleanor Pullenayegum [d,e,f], Charlie H. Goldsmith [d,e,f], Lehana Thabane [d,e,f,g,*]

[a] Department of Mathematics and Statistics, McMaster University, Hamilton, Ontario, Canada
[b] Department of Kinesiology, University of Waterloo, Waterloo, Ontario, Canada
[c] Division of Clinical Pharmacology & Therapeutics, Department of Medicine, McMaster University, Canada
[d] Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada
[e] Biostatistics Unit, St Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
[f] The Centre for Evaluation of Medicines, St Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada
[g] Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada

Data withdrawal is addressed in **Chapter 3: Consent Process; Article 3.7B**: "Participants in such research must have the opportunity to refuse consent and request the withdrawal of their data and/or human biological materials whenever possible, practicable and appropriate (Article 3.1)."

Tri-Council Policy Statement

Ethical Conduct for Research Involving Humans

TCPS2 2018

Canadian Institutes of Health Research
Natural Sciences and Engineering Research Council of Canada
Social Sciences and Humanities Research Council

Government of Canada / Gouvernement du Canada

Canada

However,….

"REBs must also consider whether the option to withdraw data is appropriate. In some types of research, permitting the withdrawal of data and/or human biological materials could skew the results of the research, invalidating the study and denying potential benefits to society. The

invalidation of study findings may also demonstrate a lack of respect for the contributions made by other participants"

What are the frequently asked questions

about missing data?

- How small a % of missing data to make it ignorable?
  - ✓ It depends!

- ✓ On size of study, reasons for missing, pattern of missingness
  - ❑ How large a % of missing to make it worthless to impute?
- ✓ Evidence suggests that even upto 90% of missing outcome data is worth imputing

❑ What if I have missing demographic or prognostic information instead of outcome data? Will the same methods work?

- ✓ This is unresolved
- ✓ No reason to suspect that the methods won't work

❑ **For large trials, is it really worth worrying about missing data?**

- ✓ Yes, it's worth planning for regardless of the size of a study

❑ **I don't like to work with "fake" data in my study?**

- ✓ You are essentially assuming data are missing completely at random
- ✓ This has been shown to be a biased strategy

❑**Can I do posthoc imputation analysis?**

- ✓ Yes, but not ideal!
- ✓ It is best to plan for this as part of your design protocol

❑**What software can I use to perform imputation?**

- ✓ Most statistical software have MI algorithms

- ❑ **What if I don't know how to do MI imputation?**
  - ✓ Get help
  - ✓ Best to collaborate with a biostatistician from start

- ❑ **Can I assess the MAR assumption?**
  - ✓ This MAR assumption is not verifiable, because it assumes that missing data are dependent on missing data—which you don't have.

- **What about comparing the baseline characteristics of those with and without missing data to assess the MAR assumption?**
  - ✓ The comparability of baseline characteristics won't tell you anything about the comparability of missing and available outcomes
  - ✓ So, this is not a viable option for assessing MAR assumption
- **What about missing data on secondary and tertiary outcomes?**
  - ✓ The same issues apply to all outcomes regardless of whether they are primary, secondary or tertiary
- **Is there anything else I can consider?**
  - ✓ Yes, consider using time-to-event as an outcome

- ✓ Missing outcomes are censored at the last observation, and therefore corresponding patients are still included in the analysis without the need to impute

- ❑ **What about patients who died, and therefore are missing secondary outcomes after dying?**
  - ✓ Such outcome data are considered missing by design, and therefore not imputed

What are the available resources for dealing with missing data?

YALE JOURNAL OF BIOLOGY AND MEDICINE 86 (2013), pp.343-358.

FOCUS: RESEARCH AND CLINICAL ETHICS

Strategies for Dealing with Missing Data in Clinical Trials: From Design to Analysis

James D. Dziura[a,c*], Lori A. Post[a], Qing Zhao[b,c], Zhixuan Fu[b,c], and Peter Peduzzi[b,c]

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

The Prevention and Treatment of Missing Data in Clinical Trials

Roderick J. Little, Ph.D., Ralph D'Agostino, Ph.D., Michael L. Cohen, Ph.D., Kay Dickersin, Ph.D., Scott S. Emerson, M.D., Ph.D., John T. Farrar, M.D., Ph.D., Constantine Frangakis, Ph.D., Joseph W. Hogan, Sc.D., Geert Molenberghs, Ph.D., Susan A. Murphy, Ph.D., James D. Neaton, Ph.D., Andrea Rotnitzky, Ph.D., Daniel Scharfstein, Sc.D., Weichung J. Shih, Ph.D., Jay P. Siegel, M.D., and Hal Stern, Ph.D.

ELSEVIER

Check for updates

Canadian Journal of Cardiology 37 (2021) 1322–1331

Review

Missing Data in Clinical Research: A Tutorial on Multiple Imputation

Peter C. Austin, PhD,[a,b,c] Ian R. White, PhD,[d] Douglas S. Lee, MD PhD,[a,b,e,f] and Stef van Buuren, PhD[g,h]

CMAJ

ANALYSIS

Randomized trials with missing outcome data: how to analyze and what to report

Rolf H.H. Groenwold MD PhD, Karel G.M. Moons PhD, Jan P. Vandenbroucke MD PhD

The gold-standard study design to evaluate the effects of medical treatment is the randomized trial. Assignment to treatment groups is a random process, and baseline differences in prognostic factors are due to chance. Consequently, at baseline, both groups are expected to be statistically comparable with

comes were handled in the analysis, and participants with missing outcomes are typically omitted from the analysis. This results in a "complete case intention-to-treat analysis."

An example of bias due to missing

Competing interests: None declared.

This article has been peer reviewed.

Correspondence to:
Rolf Groenwold,
r.h.h.groenwold
@umcutrecht.nl

ELSEVIER

Check for updates

Journal of Clinical Epidemiology 134 (2021) 79–88

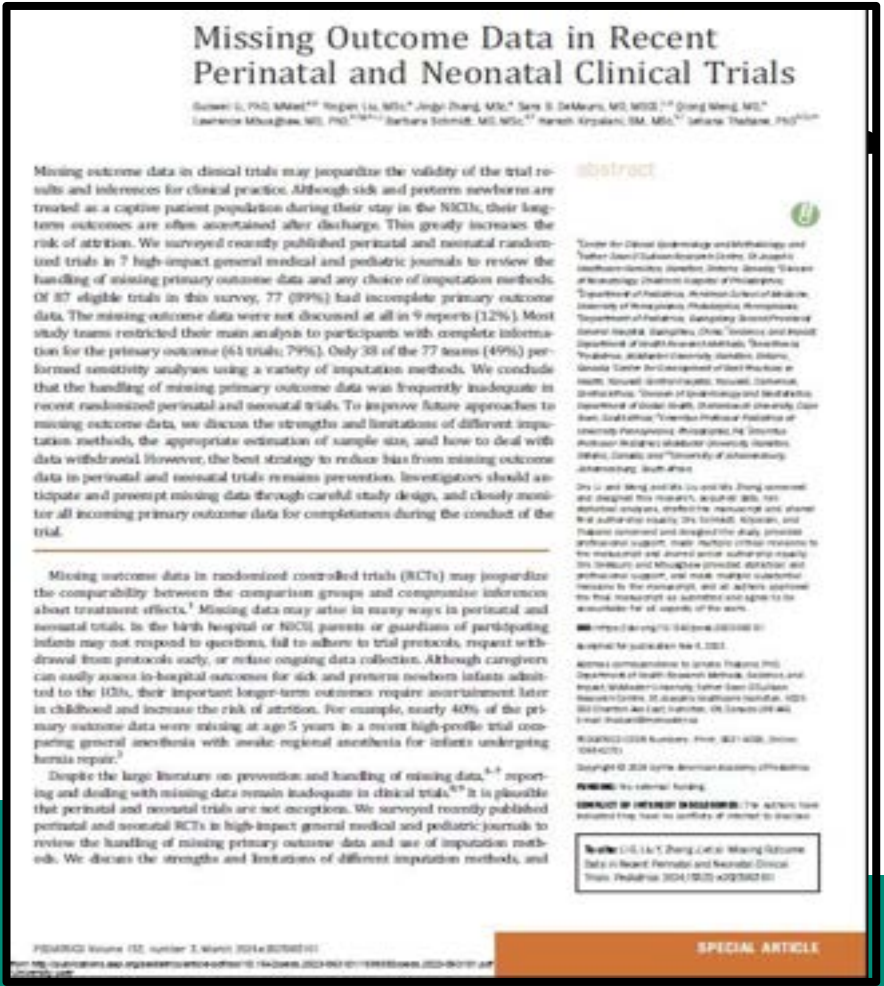
Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Framework for the treatment and reporting of missing data in observational studies: The Treatment And Reporting of Missing data in Observational Studies framework

Katherine J. Lee[a,b,*], Kate M. Tilling[c], Rosie P. Cornish[c], Roderick J.A. Little[d], Melanie L. Bell[e], Els Goetghebeur[f], Joseph W. Hogan[g], James R. Carpenter[h], on behalf of the STRATOS initiative

"This framework seeks to support researchers in thinking systematically about missing data and transparently reporting the potential effect on the study results, therefore increasing the confidence in and reproducibility of research findings".



Missing Outcome Data in Recent Perinatal and Neonatal Clinical Trials

Missing outcome data in clinical trials may jeopardize the validity of the trial results and inferences for clinical practice. Although sick and preterm newborns are treated as a captive patient population during their stay in the NICUs, their long-term outcomes are often ascertained after discharge. This greatly increases the risk of attrition. We surveyed recently published perinatal and neonatal randomized trials in 7 high-impact general medical and pediatric journals to review the handling of missing primary outcome data and any choice of imputation methods. Of 87 eligible trials in this survey, 77 (89%) had incomplete primary outcome data. The missing outcome data were not discussed at all in 9 reports (12%). Most study teams restricted their main analysis to participants with complete information for the primary outcome (61 trials; 79%). Only 38 of the 77 teams (49%) performed sensitivity analyses using a variety of imputation methods. We conclude that the handling of missing primary outcome data was frequently inadequate in recent randomized perinatal and neonatal trials. To improve future approaches to missing outcome data, we discuss the strengths and limitations of different imputation methods, the appropriate estimation of sample size, and how to deal with data withdrawal. However, the best strategy to reduce bias from missing outcome data in perinatal and neonatal trials remains prevention. Investigators should anticipate and preempt missing data through careful study design, and closely monitor all incoming primary outcome data for completeness during the conduct of the trial.

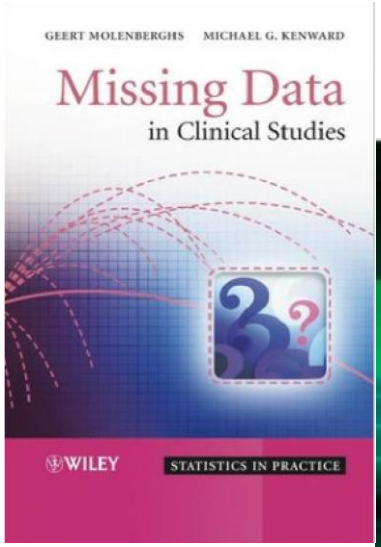
Missing outcome data in randomized controlled trials (RCTs) may jeopardize the comparability between the comparison groups and compromise inferences about treatment effects.[1]

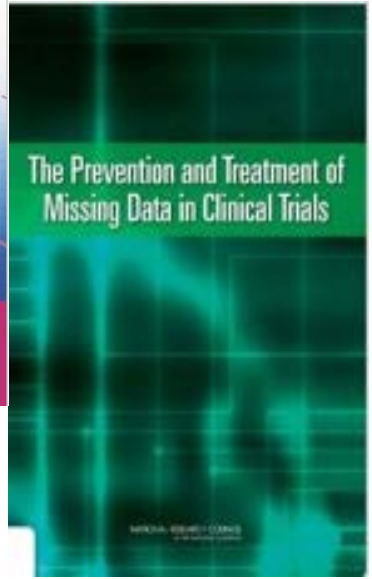
SPECIAL ARTICLE

Making the Most of Missing Data

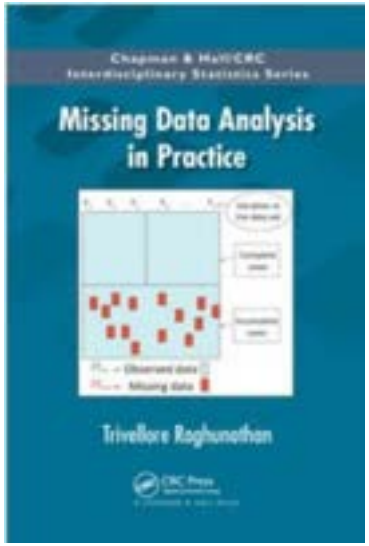
COMMENTARY

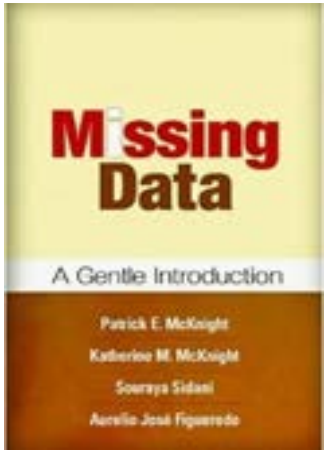
There are many textbooks on the topic


GEERT MOLENBERGHS MICHAEL G. KENWARD
Missing Data
in Clinical Studies
WILEY
STATISTICS IN PRACTICE

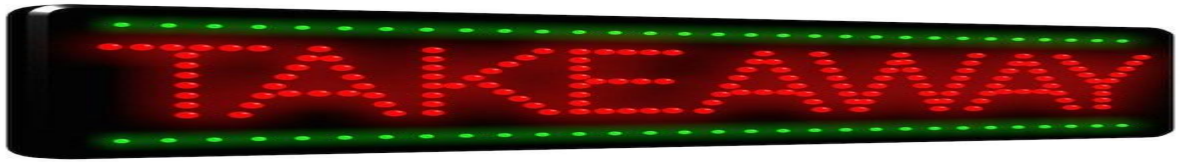

The Prevention and Treatment of
Missing Data in Clinical Trials


Applied Missing Data
Analysis in the
Health Sciences
XIAO-HUA ZHOU
CHUAN ZHOU
DANPING LIU
XIAOBO DING
STATISTICS IN PRACTICE
WILEY


Missing Data Analysis
in Practice
Trivellore Raghunathan


Missing
Data
A Gentle Introduction
Patrick E. McKnight
Katherine M. McKnight
Souraya Sidani
Aurelio José Figueredo

Please share your favorite resources for everyone to learn from



- Think about the possibility of missing data during the design and use approaches to minimize or prevent it
  - ✓ Build this into the protocol
  - ✓ Build some sensitivity analysis into the protocol to assess robustness

- Imputation can increase the efficiency and validity of the analyses
- Note that not all imputation methods work the same way—some are more efficient and less biased than others
- For most trials, ignoring missing data is not a viable option

So, what if I have some missing data or patients in my clinical trial: what's the big deal, and wouldn't imputation solve the problem?

- ✓ Big deal because of the implications on inference
- ✓ Best option is to prevent missing data

- ✓ Imputation is not a panacea, but can help as 2nd best option
- ✓ Imputation should not be used as substitute for good design and planning

The Research In[...]