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ISPOR Special Interest Group

# Workshop 12: ARE MISSING DATA PROPERLY ACCOUNTED FOR IN HEALTH ECONOMICS AND OUTCOMES RESEARCH?

## ISPOR Europe 2018 | Barcelona, Spain

Tuesday, 13 November 2018 | 15:30 – 16:30

# ISPOR Statistical Methods in HEOR Special Interest Group (SIG)

- **Mission:** To provide statistical leadership for strengthening the use of appropriate statistical methodology in health economics and outcomes research and improve the analytic techniques used in real world data analysis.

Co-Chairs of SIG

- **Rita M. Kristy, MS**, Senior Director, Medical Affairs Statistics, Astellas Pharma Global Development, Northbrook, IL, USA
- **David J. Vanness, PhD,** Professor, Health Policy and Administration, The Pennsylvania State University, State College, PA, USA

Co-Chairs of ISPOR Missing Data in HEOR Working Group

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- **Gianluca Baio, PhD, MSc,** Reader in Statistics and Health Economics, University College London (UCL), England, United Kingdom

ISPOR Special Interest Group

**David J. Vanness, PhD**
Professor, Health Policy and Administration
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# Summary of methods

# Notation and Conventions

- Let $U = (C_1, \ldots, C_n, E_1, \ldots, E_n, X_1, \ldots, X_n)$ be a vector random variable consisting of the "true" costs $C$, effectiveness measures $E$, and covariates $X$ for individuals $i = 1, \ldots N$ .
  - $C$, $E$, and $X$ are each possibly multidimensional, comprising, different types $j = 1, \ldots J$, $k = 1, \ldots K$, $l = 1, \ldots L$ and time points $t = 1, \ldots T$ of cost $c_{jt}$, outcome $e_{kt}$ and covariate $x_{lt}$measurements.
- Let $U \sim f_\theta$, where $\theta$ parameterizes the joint distribution $f$ of costs, effectiveness and covariates.
  - $\theta$ is the key object of inference for cost-effectiveness analysis

$$U \sim f_\theta$$

| Patient_ID | Date_Enroled | TX_ASSIGNED | EQ5D_VAS0 | RACE_ETHNX | EQ5D_VAS30 | EQ5D_VAS60 | EQ5D_VAS90 | SIG_AE_30 | SIG_AE_60 | SIG_AE_90 | COST_TOT |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 100054 | 1/9/2011 | Control | 73 | 3 | 71 | 59 | 53 | 0 | 1 | 0 | € 6,936 |
| 100164 | 1/1/2011 | Control | 99 | 3 | 87 | 69 | 59 | 0 | 0 | 0 | € 6,823 |
| [illegible]22 | 1/5/2011 | Control | 94 | 2 | 82 | 66 | 53 | 0 | 0 | 0 | € 7,478 |
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| 100598 | 1/3/2011 | Control | 81 | 2 | 80 | 63 | 53 | 1 | 0 | 0 | € 5,186 |
| 100748 | 1/6/2011 | Control | 98 | 1 | 98 | 87 | 70 | 0 | 0 | 0 | € 4,788 |
| 100776 | 1/1/2011 | Control | 96 | 1 | 87 | 69 | 54 | 0 | 0 | 0 | € 6,021 |
| 100816 | 1/1/2011 | Control | 93 | 1 | 81 | 66 | 55 | 0 | 0 | 1 | € 6,758 |
| 100059 | 1/1/2011 | Treat | 77 | 2 | 77 | 78 | 80 | 1 | 0 | 0 | € 11,458 |
| 100102 | 1/9/2011 | Treat | 92 | 1 | 86 | 89 | 85 | 0 | 0 | 0 | € 8,746 |
| 100139 | 1/9/2011 | Treat | 78 | 4 | 76 | 69 | 68 | 0 | 1 | 0 | € 9,711 |
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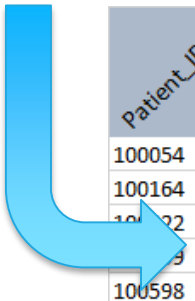
| 100856 | 1/1/2011 | Treat | 83 | 1 | 84 | 82 | 82 | 0 | 1 | 0 | € 6,656 |

# Notation and conventions (continued)

- Let M = $(m_{c111}, \ldots m_{cJTN}, m_{e111}, \ldots, m_{eKTN}, m_{x111}, \ldots, m_{xLTN})$ be a vector variable of binary missing-data indicators, where for example, $m_{cjti} = 0$ if cost type $j$ is missing for subject $i$ at time $t$, and = 1 if it is observed.
  - Let $\mathrm{M} \sim \pi_{\phi}$, where $\phi$ parameterizes the 'process that causes missing data' (Rubin DB. Inference and missing data. Biometrika 1976;63:581–592.)
- Let $V = M \cdot U + (1 - M) \cdot \mathrm{NA}$ be the vector variable of outcomes and covariates as collected, with unobserved values replaced by "NA".
- Given an actual realization of a missing data pattern $\tilde{m}$, partition each element of $U$ (the "true" data) and of $V$ (the "collected" data) into components $(u_0, u_1)$ and $(v_0, v_1)$ corresponding to values where $\tilde{m} = 0$ (missing), and $\tilde{m} = 1$ (observed), respectively.
  - $\tilde{u}_{(1)} = \tilde{v}_{(1)}$ is known, but $\tilde{u}_{(0)}$ is unobserved.

$$V \sim \pi_\phi \circ f_\theta$$



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$$V \sim \pi_\phi \circ f_\theta$$

$\tilde{m} = 0$

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$\tilde{v}_{(1)}$ $\tilde{v}_{(0)}$

$$U \sim f_\theta$$

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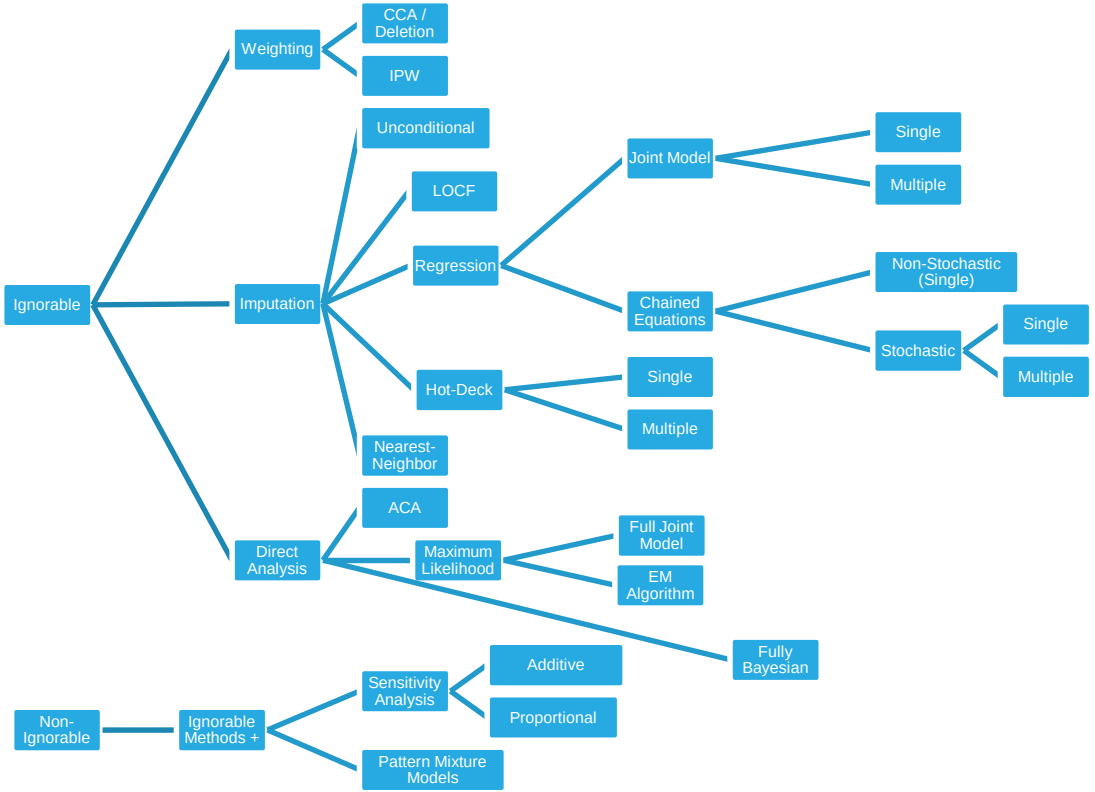
$\tilde{u}_{(1)}$ $\tilde{u}_{(0)}$

**Key Question: what can we infer about the $f_\theta$ that generates true data $U$ given that we observe $\pi_\phi \circ f_\theta$ that generates the collected data $V$?**

- Ignorable missingness:
  - $\pi_\phi \perp\!\!\!\perp f_\theta$: the process that generates the missingness is distinct from the process that generates the true data. (Missing Completely At Random – **MCAR**)
  - $\pi_\phi \perp\!\!\!\perp f_\theta \,|\tilde{v}_{(1)}$: the process that generates the missingness is distinct from the process that generates the true data, conditional on the observed data. (Missing at Random – **MAR**)
- Non-ignorable missingness
  - $\pi_\phi \perp\!\!\!\perp f_\theta \,|(\tilde{v}_{(1)}, \tilde{u}_{(0)})$ : the process that generates the missingness is only distinct from the process that generates the true data after conditioning on observed and unobserved data. (Missing Not at Random – **MNAR**)
  - Means we cannot "ignore" the process that generated the missing data.

# A taxonomy of approaches to missing data:



**Necdet Gunsoy, PhD, MPH**
Director, Analytics and Innovation GlaxoSmithKline (GSK)

# How is missing data accounted for in HEOR?

# What is special about HEOR?

Regulatory literature is mostly focussed on missing data for clinical outcomes

Most HEOR is focussed upon cost, health-related quality of life (HRQoL), and utility data

- Cost and utility data have very particular distributions (e.g. highly skewed cost data with many 0s, EQ-5D index data with many 1s)
- Cost and utility/HRQoL can be strongly correlated (e.g. 0 cost associated with high utility)

HEOR requires more tailored approaches to report and account for missing data

# What is special about HEOR?

HEOR requires more tailored approaches to report and account for missing data

But very few studies focus on missing data for HEOR

# Missing data methods in HEOR

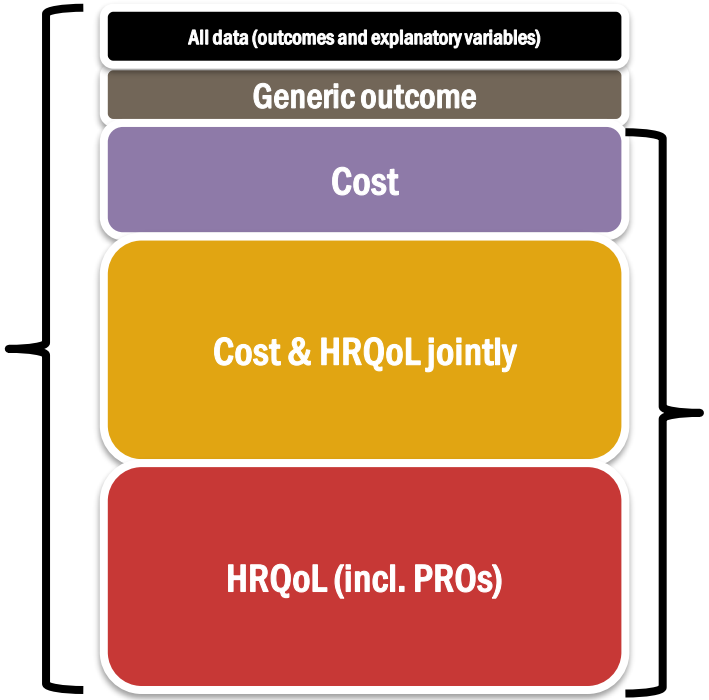
- A literature review was conducted to understand methodological approaches used to account for missing data in cost-effectiveness analyses (CEA)

- 16 studies were identified

# Missing data methods in HEOR

- 16 studies were identified

What type of missing data was addressed?

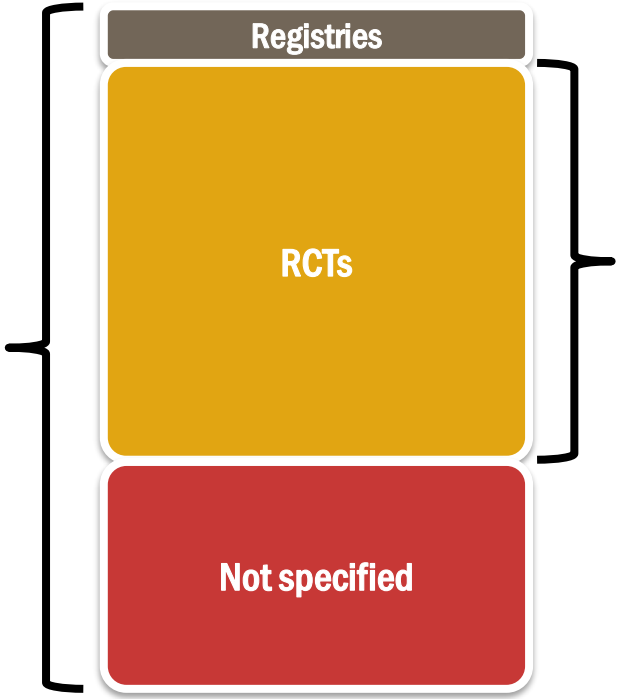



The majority of studies looked at cost and/or HRQoL specifically

# Missing data methods in HEOR

- 16 studies were identified

In what context was missing data addressed?

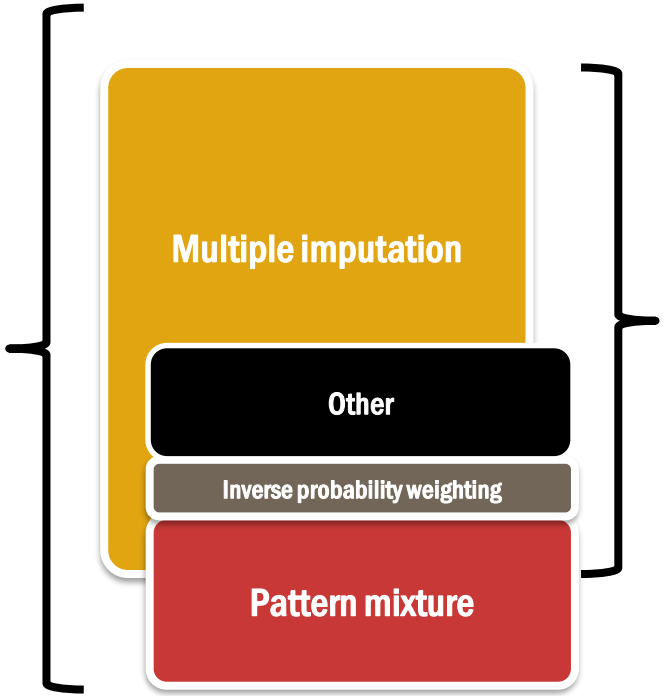



The majority of studies looked at economic evaluations alongside RCTs

# Missing data methods in HEOR

- 16 studies were identified

What type of method was used to address missing data?




9 studies used multiple imputation

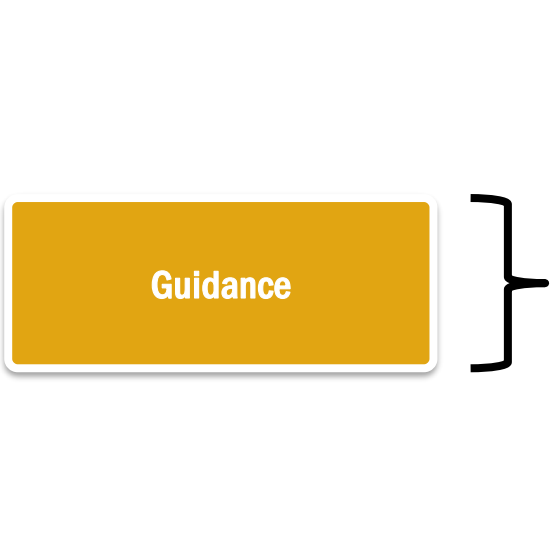
>10 different types of MI approaches were investigated

NOTE: some articles were review articles or provided general guidance

# Missing data methods in HEOR

- 16 studies were identified

Was any guidance provided in the use of methods to account for missing data?




3 studies provided practical guidance

# Missing data methods in HEOR

- Few studies have investigated methodological approach to account for missing data specifically in the context of CEA
- The majority of studies are focussed on outcomes (vs. also explanatory factors), data from RCTs, and on MI method
- There was a large variety of data manipulation and MI methods used

**Nneka Onwudiwe, MBA, PharmD, PhD**
Senior Scientific Reviewer
US Food and Drug Administration

# Overview of Guidance

# Professional Biography

**Dr. Nneka C. Onwudiwe**
*PRO/PE Senior Scientific Reviewer*

Nneka C. Onwudiwe, PhD, PharmD, MBA received her doctorate in Pharmacy (PharmD) from the University of Maryland School of Pharmacy, PhD in Health Services Research with a specialization in Pharmacoeconomics from the University of Maryland School of Pharmacy, and a MBA (Honors) from the University of Baltimore. In addition, she received an honor of Rho Chi in Pharmacy in 2002 and an honor of Beta Gamma Sigma in Business Administration in 2012.

Dr. Onwudiwe is a Patient-reported outcomes (PRO) and Pharmacoeconomics (PE) Regulatory Review Officer at the Food and Drug Administration (FDA). Dr. Onwudiwe is the technical expert and point of contact in the review of PRO, PE, and other type of claims in prescription drug promotion for the Division of Advertising and Promotion Review II (DAPR II) within the Office of Prescription Drug Promotion.

Dr. Onwudiwe teaches Comparative Effectiveness Research (CER) & Pharmacoeconomics at the University of Maryland School of Pharmacy. Dr. Onwudiwe has received several awards and accolades over the years. She has received funding as a Principal Investigator from NIH/NHLBI. Dr. Onwudiwe currently serves on the Food and Drug Law Institute's (FDLI) Publications Peer Review Committee as well as a member of the ISPOR Value Assessment Frameworks Stakeholder Advisory Panel.

Dr. Onwudiwe has served on several ISPOR Scientific and Health Policy Working Groups (Task Forces and Special Interest Groups) that have developed products and tools used by decision makers and researchers around the world. She is currently serving on the Value Assessment of Medical Device Special Interest Group and Statistical Methods in Health Economics and Outcomes Research Special Interest Group. In addition to this work, Dr. Onwudiwe has presented at various professional conferences and published in several peer-reviewed journals such as *Value in Health Regional Issues, Spine, Journal of the American Medical Association (JAMA), Obesity, Oncologist, Cancer Medicine, and Ethnicity and Disease.*

Dr. Onwudiwe is founder and CEO of Pharmaceutical Economics Consults of America (PEÇA) and holds a license in pharmacy and practices in the community providing medication therapy management (MTM) and other services.

# Disclaimer

*"The views expressed in this presentation are those of the speaker. Therefore, nothing in this presentation should be construed to represent FDA's views or policies."*

# Terminology

- Missingness—the existence of missing data and the mechanism that explains the reason for the data being missing
- Missing data mechanisms
  - MCAR
  - MAR
  - MNAR
- Proportion of missing data— directly related to the quality of statistical inferences
- Missing data occur at two levels
  - Unit level or item level
- Patterns of missing data
  - Univariate, monotone, arbitrary
- Statistical methods
  - Direct imputation (LOCF, BOCF), MMRM, MI, weighting, etc.
- Assumptions and patterns of missingness to determine statistical methods
  - MCAR, MAR, MNAR
  - assumptions of analytic models

- To provide a practical guidance on how to handle missing data in within-trial CEAs:
  - the analysis should be based on a plausible assumption for the missing data mechanism
  - the method chosen for the base-case should fit with the assumed mechanism
  - sensitivity analysis should be conducted to explore to what extent the results change with the assumption made

PharmacoEconomics (2014) 32:1157–1170
DOI 10.1007/s40273-014-0193-3

PRACTICAL APPLICATION

# A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials

Rita Faria · Manuel Gomes · David Epstein · Ian R. White

Published online: 29 July 2014


**Abstract** Missing data are a frequent problem in cost-effectiveness analysis (CEA) within a randomised controlled trial. Inappropriate methods to handle missing data can lead to misleading results and ultimately can affect the decision of whether an intervention is good value for money. This article provides practical guidance on how to handle missing data in within-trial CEAs following a principled approach: (i) the analysis should be based on a plausible assumption for the missing data mechanism, i.e. whether the probability that data are missing is independent of or dependent on the observed and/or unobserved values; (ii) the method chosen for the base-case should fit with the assumed mechanism; and (iii) sensitivity analysis should be conducted to explore to what extent the results change with the assumption made. This approach is implemented in three stages, which are described in detail: (1) descriptive analysis to inform the assumption on the missing data mechanism; (2) how to choose between alternative methods given their underlying assumptions; and (3) methods for sensitivity analysis. The case study illustrates how to apply this approach in practice, including software code. The article concludes with recommendations for practice and suggestions for future research.

**Key Points for Decision Makers**

Missing data are a frequent problem in cost-effectiveness analysis within a randomised clinical trial.

Different methods of handling missing data can yield different results and affect decisions on the value for money of healthcare interventions.

The choice of method should be grounded in the assumed missing data mechanism, which in turn should be informed by the available evidence.

The impact of alternative assumptions about the missing data mechanism should be carefully assessed in sensitivity analysis.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40273-014-0193-3) contains supplementary material, which is available to authorized users.

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## 1 Introduction

Decisions on whether new interventions are cost effective and should be offered by healthcare services are often informed by a cost-effectiveness analysis (CEA) undertaken within a randomised controlled trial (RCT), referred to as a within-trial CEA. Missing data occur frequently in RCTs: patients may be lost to follow-up, questionnaires may be lost or unreturned and responses to individual

- Three stages in the analysis:
- Stage 1– descriptive analysis to inform the assumption on the missing data mechanism
  - amount of missing data by trial group at each follow-up period
  - missing data patterns
  - association between missingness and baseline variables
  - association between missingness and observed outcomes
- Stage 2–how to choose between alternative methods given their underlying assumptions
  - should fit with the assumption regarding the missing data mechanism and account for the uncertainty
  - handle the particular characteristics of CEA data

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- Stage 2—how to choose, cont'd.
  - Missing Baseline Values
    - mean imputation and MI are suggested options
  - Complete Case Analysis, Available Case Analysis and Inverse Probability Weighting
    - CCA are valid under MCAR
    - IPW is suitable for a monotonic pattern of missing data
  - Single Imputation
    - mean imputation valid for missing baseline variables
    - Last-value carried forward (LVCF) can bias parameter estimates
    - single imputation methods are not appropriate to handle missing data on outcomes
  - Multiple Imputation
    - MI can handle both monotonic and nonmonotonic missing data under MAR and can be modified to handle MNAR
    - two approaches to implementing MI: joint modelling (MI-JM) and chained equations (MICE)
      - MI-JM assumes multivariate normal distribution
      - MICE accommodates non-normal distributions

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**Abstract** Missing data are a frequent problem in cost-effectiveness analysis (CEA) within a randomised controlled trial. Inappropriate methods to handle missing data can lead to misleading results and ultimately can affect the decision of whether an intervention is good value for money. This article provides practical guidance on how to handle missing data in within-trial CEAs following a principled approach: (i) the analysis should be based on a plausible assumption for the missing data mechanism, i.e. whether the probability that data are missing is independent of or dependent on the observed and/or unobserved values; (ii) the method chosen for the base-case should fit with the assumed mechanism; and (iii) sensitivity analysis should be conducted to explore to what extent the results change with the assumption made. This approach is implemented in three stages, which are described in detail: (1) descriptive analysis to inform the assumption on the missing data mechanism; (2) how to choose between alternative methods given their underlying assumptions; and (3) methods for sensitivity analysis. The case study illustrates how to apply this approach in practice, including software code. The article concludes with recommendations for practice and suggestions for future research.

**Key Points for Decision Makers**

Missing data are a frequent problem in cost-effectiveness analysis within a randomised clinical trial.

Different methods of handling missing data can yield different results and affect decisions on the value for money of healthcare interventions.

The choice of method should be grounded in the assumed missing data mechanism, which in turn should be informed by the available evidence.

The impact of alternative assumptions about the missing data mechanism should be carefully assessed in sensitivity analysis.

**Electronic supplementary material** The online version of this article (doi:10.1007/s40273-014-0193-3) contains supplementary material, which is available to authorized users.

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## 1 Introduction

Decisions on whether new interventions are cost effective and should be offered by healthcare services are often informed by a cost-effectiveness analysis (CEA) undertaken within a randomised controlled trial (RCT), referred to as a within-trial CEA. Missing data occur frequently in RCTs: patients may be lost to follow-up, questionnaires may be lost or unreturned and responses to individual

- Stage 2—how to choose, cont'd.
  - Likelihood-Based Methods
    - Likelihood-based models assume MAR conditional on the variables
    - Likelihood-based methods can produce similar results to MI
    - rely on the correct specification of
    - the model, including its parametric assumptions
      - wrong specification of the model may impact results
- Stage 3—methods for sensitivity analysis to MAR
  - selection models and pattern mixture approaches
  - Selection models using a weighting approach tends to fail for large departures from MAR

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PRACTICAL APPLICATION

# A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials

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**Table 4** Recommendations for practice

| Recommendation | Comments |
|---|---|
| Stage 1: Descriptive analysis | |
| 1.1 Conduct descriptive analysis of the data:<br>• Proportion of missing data by trial group at each follow-up period<br>• Missing data pattern<br>• Association between missingness and baseline variables<br>• Association between missingness and observed outcomes | Report the descriptive analysis that was conducted to inform the assumption on the missing data mechanism |
| 1.2 Discuss among the trial team (trialists, clinicians, trial management group, etc.) the possible mechanisms and reasons for missing data | |
| 1.3 Make an assumption on the missing data mechanism based on the information collected in 1.1 and 1.2 | Note that the descriptive analysis can distinguish between MCAR, CD-MCAR and MAR, but it cannot rule out MNAR |
| 1.4 State the assumption on the missing data mechanism and justify the choice of assumption | |
| 1.5 Report HR-QOL, resource use and costs (if applicable) by treatment group prior to imputation | |
| Stage 2: Choosing and Implementing a Method to Handle Missing data | |
| 2.1. Choose a method to handle the missing data in accordance with the assumed missing data mechanism | Complete case analysis (with the baseline covariates related with missing data included in the analysis model) for CD-MCAR, MI or likelihood-base model for MAR, IPW for monotonic missing data under MCAR, CD-MCAR or MAR |
| 2.2. State up front any other assumptions required for the analysis | e.g. whether missing data in individual resource use items are assumed to be zero |
| 2.3. Include all randomised individuals with follow-up data | Individuals with data only at baseline may be excluded from the base case but should be included in a scenario to make the analysis truly intention-to-treat |
| 2.4. Impute missing baseline covariates with mean imputation or MI | MI is more complex, and may be less efficient, than mean imputation |
| 2.5. MI seems the most widely applicable method of analysis:<br>• The imputation model should include all covariates related to missingness, related to outcomes and any variable included in the analysis model<br>• MI should be implemented separately by treatment allocation<br>• The number of imputations should be at least greater than the proportion of missing data<br>• Predictive mean matching and/or transformations in MICE can help with CEA data that is non-normal distributed<br>• Costs can be imputed at a resource use level or as costs<br>• QALYs can be imputed at HR-QOL domain level, at the index score level or as QALYs | MI can be implemented with chained equations (MI-MICE) or by joint modelling (MI-JM), which assumes multivariate normality. The current evidence base does not allow for strict recommendations for one approach over another |
| 2.6. Likelihood-based models are a sensible alternative to MI but can be more difficult to implement | Likelihood-based models avoid the imputation step but only covariates allowed for the analysis model can be included. They can be difficult to implement when costs or health outcomes are disaggregated |
| 2.7. IPW methods are useful if the missing data pattern is monotonic | IPW avoids the imputation step but its reliability is dependent on the model specification |
| 2.8. Other ad hoc methods (e.g. complete case, mean imputation or last-value carried forward) should be avoided | They cannot incorporate the uncertainty inherent in missing data, and often make implausible assumptions about the missing data mechanism |
| 2.9. The method chosen to handle missing data can be validated by comparing results with an alternative method that makes the same assumption on the missing data mechanism (e.g. likelihood-based model vs. MI with the same covariates) | If using MI, the imputation model can be validated by comparing the distribution of observed and imputed data |

Table 4 continued

| Recommendation | Comments |
|---|---|
| 2.10. If using MI, report resource use, HR-QOL scores (if imputed at this level), costs and QALYs by treatment group after imputation. Results after imputation should be compared with the descriptive analysis pre-imputation | |
| Stage 3: Sensitivity analysis to the MAR assumption | |
| 3.1. Sensitivity analysis explores the robustness of the results to alternative assumptions on the missing data mechanism: | Pattern mixture and selection models can be difficult to implement |
| • The methods proposed here (weighting approach or an additive shift of imputed values) are straightforward and informative | |
| 3.2. Interpret the results of the sensitivity analysis in light of the understanding of the disease and the trial context (see 1.2.) | Does the allocation decision (i.e. is the intervention likely to be cost effective?) change given plausible changes in the assumption on the missing data mechanism? |

*CD-MCAR* covariate-dependent missing completely at random, *CEA* cost-effectiveness analysis, *HR-QOL* health-related quality of life, *IPW* inverse probability weighting, *MAR* missing at random, *MCAR* missing completely at random, *MI* multiple imputation, *MI-JM MI: joint modelling*, *MI-MICE* MI: chained equations, *MNAR* missing not at random, *QALYs* quality-adjusted life-years

- This article reviews how missing cost-effectiveness data were addressed in trial-based CEA by examining:
  - the extent of missing data
  - how these were addressed in the analysis
  - whether sensitivity analyses to different missing data assumptions were performed
- The article also provides a critical review of findings and recommendations to improve practice

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HEALTH ECONOMICS LETTER

WILEY Health Economics

# Missing data in trial-based cost-effectiveness analysis: An incomplete journey

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**SUMMARY**
Cost-effectiveness analyses (CEA) conducted alongside randomised trials provide key evidence for informing healthcare decision making, but missing data pose substantive challenges. Recently, there have been a number of developments in methods and guidelines addressing missing data in trials. However, it is unclear whether these developments have permeated CEA practice. This paper critically reviews the extent of and methods used to address missing data in recently published trial-based CEA.
Issues of the Health Technology Assessment journal from 2013 to 2015 were searched. Fifty-two eligible studies were identified. Missing data were very common; the median proportion of trial participants with complete cost-effectiveness data was 63% (interquartile range: 47%–81%). The most common approach for the primary analysis was to restrict analysis to those with complete data (43%), followed by multiple imputation (30%). Half of the studies conducted some sort of sensitivity analyses, but only 2 (4%) considered possible departures from the missing-at-random assumption.
Further improvements are needed to address missing data in cost-effectiveness analyses conducted alongside randomised trials. These should focus on limiting the extent of missing data, choosing an appropriate method for the primary analysis that is valid under contextually plausible assumptions, and conducting sensitivity analyses to departures from the missing-at-random assumption.

**KEYWORDS**
cost-effectiveness analysis, missing data, multiple imputation, randomised controlled trials, sensitivity analysis

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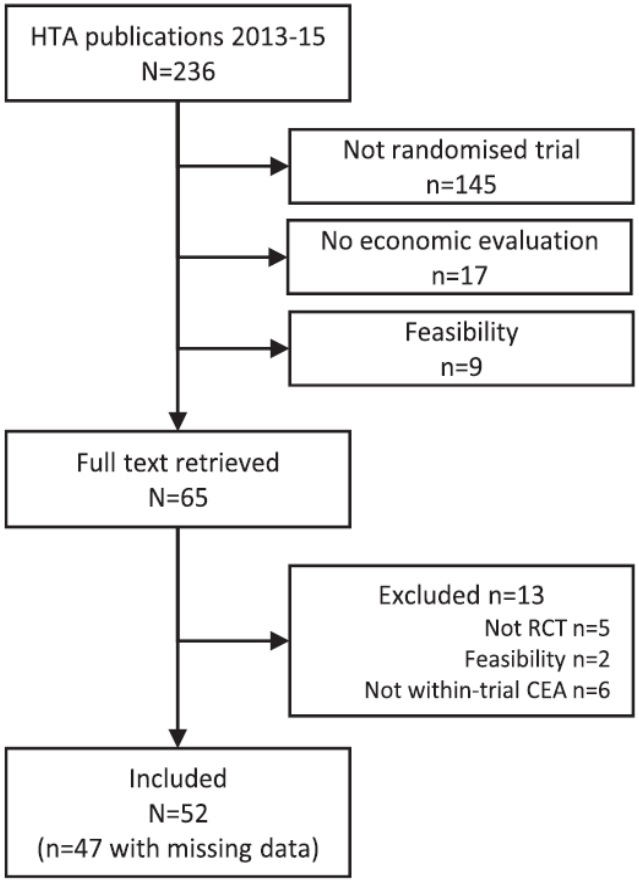


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**TABLE 1** Characteristics of included studies ($n = 52$)

| | *n* Median | % (IQR) |
|---|---|---|
| **General characteristics** | | |
| Publication year | | |
| 2013 | 14 | 27 |
| 2014 | 15 | 29 |
| 2015 | 23 | 44 |
| CEA time frame | | |
| 0–11 months | 22 | 42 |
| 12 months | 19 | 37 |
| ≥24 months | 11 | 21 |
| Follow-up design | | |
| Continuous (time to event) | 4 | 8 |
| One follow-up assessment | 11 | 21 |
| Repeated assessments | 37 | 71 |
| Effectiveness measure | | |
| QALY | 42 | 81 |
| Binary | 6 | 12 |
| Clinical scale score | 3 | 6 |
| Time to recovery | 1 | 2 |
| **Missing data** | | |
| Report exact number of complete cases | 20 | 38 |
| Proportion of complete cases[a] | 0.63 | (0.47–0.81) |
| Proportion complete effectiveness data ($n = 47$) | 0.73 | (0.55–0.86) |
| Proportion complete cost data ($n = 40$) | 0.79 | (0.67–0.92) |
| Differs between costs and effectiveness[b] | | |
| Yes, more cost data missing | 3 | 6 |
| Yes, more effect data missing | 10 | 19 |
| No | 22 | 42 |
| No missing (<5%) | 5 | 10 |
| Unclear | 12 | 23 |
| Differs between arms[c] | | |
| Yes | 10 | 19 |
| No | 32 | 62 |
| No missing (<5%) | 5 | 10 |
| Unclear | 5 | 10 |

*Note.* IQR = interquartile range; QALY = quality-adjusted life year.

[a]Proportion of trial participants with complete cost-effectiveness data. An upper bound was used if exact number not reported.

[b]More than 5% difference in the proportion of participants with complete cost or effectiveness data.

[c]More than 5% difference in the proportion of complete cases between arms.

**TABLE 2** Methods for handling missing data in primary analysis ($n = 47$)

| Primary analysis method | *n* | % |
|---|---|---|
| Complete-case analysis | 20 | 43 |
| Multiple imputation | 14 | 30 |
| Other—single methods | | |
| Inverse probability weighting | 1 | 2 |
| Bayesian model, missing data as unknown parameter | 1 | 2 |
| Other—ad hoc hybrid methods[a] | 8 | 17 |
| Using a combination of | | |
| Mean imputation[b] | 6 | |
| Regression imputation[c] | 3 | |
| Inverse probability weighting[d] | 2 | |
| Assuming failure when outcome missing | 2 | |
| Multiple imputation | 1 | |
| Last observation carried forward | 1 | |
| Unclear | 3 | 6 |

[a]Ad hoc hybrid method = several approaches to missing data combined, for example, using mean imputation for missing individual resource use items and multiple imputation for fully incomplete observations.

[b]Mean imputation = replacing missing values by the average across other participants.

[c]Regression imputation = replace missing values by predicted value based on observed variables.

[d]Inverse probability weighting = analysing complete data, weighted according to their modelled probability of being observed. These methods are presented in more details in other references (Baio & Leurent, 2016; Faria et al., 2014).

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Issues of the Health Technology Assessment journal from 2013 to 2015 were searched. Fifty-two eligible studies were identified. Missing data were very common; the median proportion of trial participants with complete cost-effectiveness data was 63% (interquartile range: 47%–81%). The most common approach for the primary analysis was to restrict analysis to those with complete data (43%), followed by multiple imputation (30%). Half of the studies conducted some sort of sensitivity analyses, but only 2 (4%) considered possible departures from the missing-at-random assumption.

Further improvements are needed to address missing data in cost-effectiveness analyses conducted alongside randomised trials. These should focus on limiting the extent of missing data, choosing an appropriate method for the primary analysis that is valid under contextually plausible assumptions, and conducting sensitivity analyses to departures from the missing-at-random assumption.

**KEYWORDS**

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**TABLE 3** Approaches to missing data, by year, number of follow-ups, and extent of missing data ($n = 47$)

| | Primary analysis method | | | | | | Reported a sensitivity analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | CCA | | MI | | Other | | Yes | | No | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| Publication year | | | | | | | | | | |
| 2013 ($n = 13$) | 6 | 46 | 3 | 23 | 4 | 31 | 5 | 38 | 8 | 62 |
| 2014 ($n = 15$) | 9 | 60 | 1 | 7 | 5 | 33 | 6 | 40 | 9 | 60 |
| 2015 ($n = 19$) | 5 | 26 | 10 | 53 | 4 | 21 | 11 | 58 | 8 | 42 |
| Number of follow-up assessments[a] | | | | | | | | | | |
| 1 ($n = 10$) | 7 | 70 | 1 | 10 | 2 | 20 | 3 | 30 | 7 | 70 |
| ≥2 ($n = 36$) | 13 | 36 | 13 | 36 | 10 | 28 | 18 | 50 | 18 | 50 |
| Proportion of complete cases[b] | | | | | | | | | | |
| <50% ($n = 15$) | 4 | 27 | 6 | 40 | 5 | 33 | 8 | 53 | 7 | 47 |
| 50–75% ($n = 18$) | 10 | 56 | 4 | 22 | 4 | 22 | 9 | 50 | 9 | 50 |
| 75%–95% (n = 14) | 6 | 43 | 4 | 29 | 4 | 29 | 5 | 36 | 9 | 64 |
| Information missing[c] | | | | | | | | | | |
| Similar ($n = 22$) | 13 | 59 | 6 | 27 | 3 | 14 | 10 | 45 | 12 | 55 |
| More cost missing ($n = 3$) | 1 | 33 | 2 | 67 | 0 | 0 | 2 | 67 | 1 | 33 |
| More effect missing ($n = 10$) | 4 | 40 | 2 | 20 | 4 | 40 | 6 | 60 | 4 | 40 |

*Note.* % = row percentages. CCA = complete-case analysis; MI = multiple imputation.

[a]Excluding one study with continuous follow-up ($n = 46$).

[b]For the five studies with less than 5% of incomplete cases, four used CCA and one an ad hoc hybrid method for their primary analysis. One of the five studies conducted a sensitivity analysis to missing data.

[c]Excluding 12 studies where this was unclear ($n = 35$).

**TABLE 4** Sensitivity analysis, overall, and by primary analysis method ($n = 47$)

| | Sensitivity analysis method | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | None | | CCA | | MI (MAR) | | MNAR | | Other[a] | |
| | *n* | % | *n* | % | *n* | % | *n* | % | *n* | % |
| **Overall** | | | | | | | | | | |
| Total ($n = 47$) | 25 | 53 | 11 | 23 | 9 | 19 | 2 | 4 | 5 | 11 |
| **By primary analysis** | | | | | | | | | | |
| CCA (n = 20) | 10 | 50 | 0 | 0 | 8 | 40 | 0 | 0 | 2 | 10 |
| MI (n = 14) | 5 | 36 | 9 | 64 | 0 | 0 | 2 | 14 | 2 | 14 |
| Other (n = 13) | 10 | 77 | 2 | 15 | 1 | 8 | 0 | 0 | 1 | 8 |

*Note.* % = row percentages; CCA = complete-case analysis; MAR = assuming data missing at random; MI = multiple imputation; MNAR = assuming data missing not at random. Total may be more than 100% as some studies conducted more than one sensitivity analysis.

[a]Other methods used for sensitivity analysis include last observation carried forward ($n = 1$), regression imputation ($n = 1$), adjusting for baseline predictors of missingness ($n = 1$), imputing by average of observed values for that patient ($n = 1$), and an ad hoc hybrid method using multiple and mean imputation ($n = 1$).

**TABLE 5** Review of indicators based on recommendations criteria ($n = 47$)

| Criterion[a] | Met[b] | | Not met | | Unclear | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| **Prevent** | | | | | | |
| A1. Maximise response rate | 35 | 74 | 12 | 26 | 0 | 0 |
| A2. Alternative data sources | 10 | 21 | 37 | 79 | 0 | 0 |
| A3. Monitor completeness | 17 | 36 | 30 | 64 | 0 | 0 |
| **Primary** | | | | | | |
| B1. Assumption for primary analysis | 17 | 36 | 27 | 57 | 3 | 6 |
| B2. Appropriate primary method | 17 | 36 | 27 | 57 | 3 | 6 |
| **Sensitivity** | | | | | | |
| C1. Discuss departures from the primary assumption | 0 | 0 | 47 | 100 | 0 | 0 |
| C2. Consider broad range of assumptions | 2 | 4 | 45 | 96 | 0 | 0 |
| C3. Method valid under these assumptions | 2 | 4 | 45 | 96 | 0 | 0 |
| **Report** | | | | | | |
| D1. Missing data by endpoint, arm, and time point | 29 | 62 | 18 | 38 | 0 | 0 |
| D2. Discuss reasons for missing data | 16 | 34 | 31 | 66 | 0 | 0 |
| D3. Describe methods used and assumptions | 17 | 36 | 30 | 64 | 0 | 0 |
| D4. Conclusions in light of missing data | 1 | 2 | 46 | 98 | 0 | 0 |

[a]See Figure 3 and Appendix B for definition of each criterion.

[b]Report demonstrates evidence of having followed this recommendation. *Not met* if the recommendation was not followed or not mentioned. *Unclear* if some suggestions the criteria may have been met but information not clear enough. See Appendix B for detailed definitions and methodology used.

# Recommendations

- Alternative sources should also be considered to minimize missing information, for example, administrative data or electronic health records
- Report details of the pattern of missing data
- The choice of CCA for the primary analysis approach is difficult to justify in the presence of repeated measurements
- Consider approaches valid under more plausible MAR assumptions and making use of all the observed data, such as
  - MI
  - Likelihood-based repeated measures models
  - Bayesian models
- Appropriate methods for sensitivity analysis
  - Selection models
  - Pattern-mixture models

- **Objective**: This paper presents practical guidance on the choice of MI models for handling missing PROMs data based on the characteristics of the trial dataset. The comparative performance of complete cases analysis.

- **Methods**: Realistic missing at random data were simulated using follow-up data from an RCT considering three different PROMs (Oxford Knee Score (OKS), EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L), 12-item Short Form Survey (SF-12)). Data were multiply imputed at the item (using ordinal logit and predicted mean matching models), sub-scale and score level; unadjusted mean outcomes, as well as treatment effects from linear regression models were obtained for 1000 simulations. Performance was assessed by root mean square errors (RMSE) and mean absolute errors (MAE).

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RESEARCH ARTICLE Open Access

# Multiple imputation for patient reported outcome measures in randomised controlled trials: advantages and disadvantages of imputing at the item, subscale or composite score level

Ines Rombach[1,2*], Alastair M. Gray[1], Crispin Jenkinson[3], David W. Murray[2] and Oliver Rivero-Arias[4]

**Abstract**

**Background:** Missing data can introduce bias in the results of randomised controlled trials (RCTs), but are typically unavoidable in pragmatic clinical research, especially when patient reported outcome measures (PROMs) are used. Traditionally applied to the composite PROMs score of multi-item instruments, some recent research suggests that multiple imputation (MI) at the item level may be preferable under certain scenarios.
This paper presents practical guidance on the choice of MI models for handling missing PROMs data based on the characteristics of the trial dataset. The comparative performance of complete cases analysis, which is commonly used in the analysis of RCTs, is also considered.

**Methods:** Realistic missing at random data were simulated using follow-up data from an RCT considering three different PROMs (Oxford Knee Score (OKS), EuroQoL 5 Dimensions 3 Levels (EQ-5D-3L), 12-item Short Form Survey (SF-12)). Data were multiply imputed at the item (using ordinal logit and predicted mean matching models), sub-scale and score level; unadjusted mean outcomes, as well as treatment effects from linear regression models were obtained for 1000 simulations. Performance was assessed by root mean square errors (RMSE) and mean absolute errors (MAE).

**Results:** Convergence problems were observed for MI at the item level. Performance generally improved with increasing sample sizes and lower percentages of missing data. Imputation at the score and subscale level outperformed imputation at the item level in small sample sizes ($n \leq 200$). Imputation at the item level is more accurate for high proportions of item-nonresponse. All methods provided similar results for large sample sizes (≥500) in this particular case study.

**Conclusions:** Many factors, including the prevalence of missing data in the study, sample size, the number of items within the PROM and numbers of levels within the individual items, and planned analyses need consideration when choosing an imputation model for missing PROMs data.

**Keywords:** Missing data, Incomplete data, Questionnaires, Randomised controlled trials (RCTs), Quality of life (QoL), Domains

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# Instruments

- The 5-year follow-up data for three patient reported outcome measures:
- The Oxford Knee Score (OKS): an instrument designed to assess outcomes following a knee replacement in RCTs. It consists of 12 five level items, and the composite score ranges from 0 to 48, with higher scores indicating better outcomes.
- The SF-12: a 12-item generic health measure, with higher scores indicating better outcomes. The SF-12 generates two subscales, the physical component summary score (PCS) and the mental health component summary score (MCS).
- EQ-5D-3L: a utility questionnaire assessing participants' health state based on their mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Scores of 1 indicate full health, 0 indicates a health state equal to death, and scores lower than 0 indicate health states worse than death.

**Table 1** Missing data patterns simulated for each PROM

| OKS | | SF-12 | SF-12 | EQ-5D-3L | EQ-5D-3L |
|---|---|---|---|---|---|
| OKS missingness patterns | Observed missing data pattern | SF-12 missingness patterns | Observed missing data pattern | EQ-5D-3L missingness patterns | Observed missing data pattern |
| Unit-nonresponse | 73.1% | Unit-nonresponse | 56.1% | Unit-nonresponse | 87.9% |
| Only item 7 missing | 15.6% | Only item 2b missing | 20.3% | Only item 5 missing | 5.1% |
| Only item 4 missing | 3.3% | Only item 4b missing | 6.5% | Only item 1 missing | 2.6% |
| Only item 6 missing | 2.7% | Items 2b and 3b missing | 4.5% | Only item 4 missing | 1.8% |
| Only item 9 missing | 2.1% | Only item 3b missing | 4.0% | Only item 3 missing | 1.5% |
| Only item 10 missing | 1.5% | Items 2b, 3b and 4b missing | 3.5% | Only item 2 missing | 1.1% |
| Only item 1 missing | 0.9% | Items 2b and 4b missing | 3.3% | n/a | Other patterns occurred too infrequently to be used in simulation |
| Only item 12 missing | 0.9% | Only item 6c missing | 1.8% | n/a | |

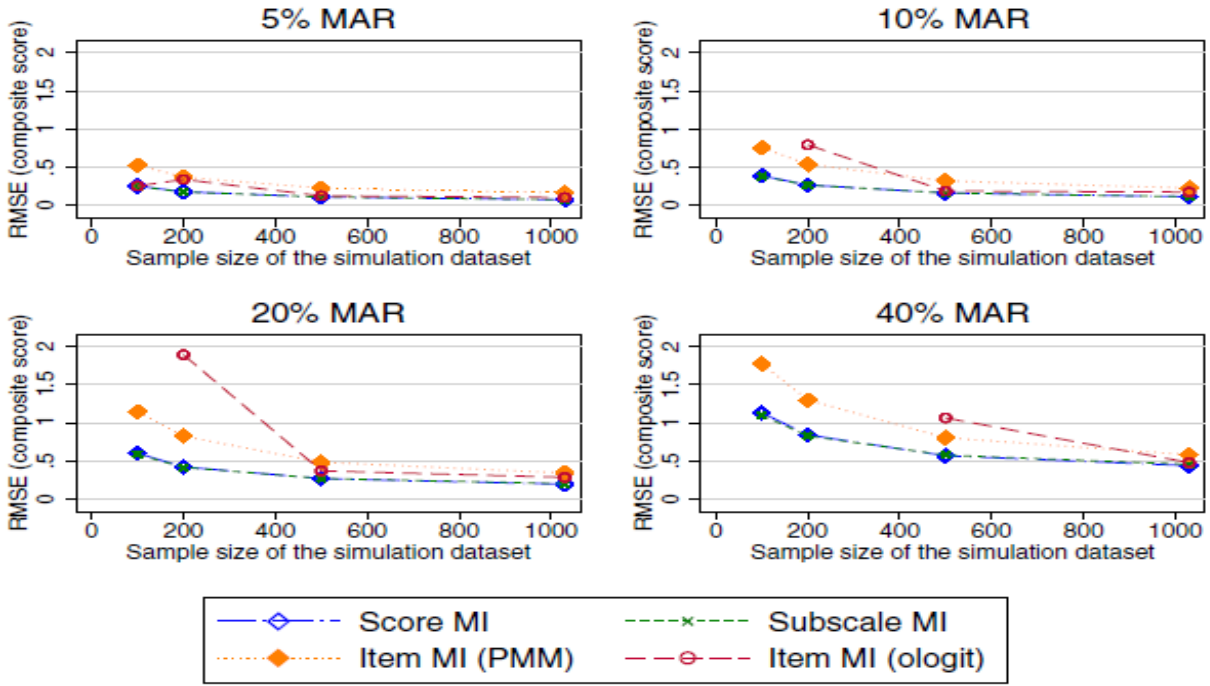


**Fig. 3** RMSE in the OKS composite score estimates (observed missing data patterns). Abbreviations: MAR – Missing at random; MI – Multiple imputation; OKS – Oxford knee score; PMM – Predicted mean matching; RMSE – Root mean square error

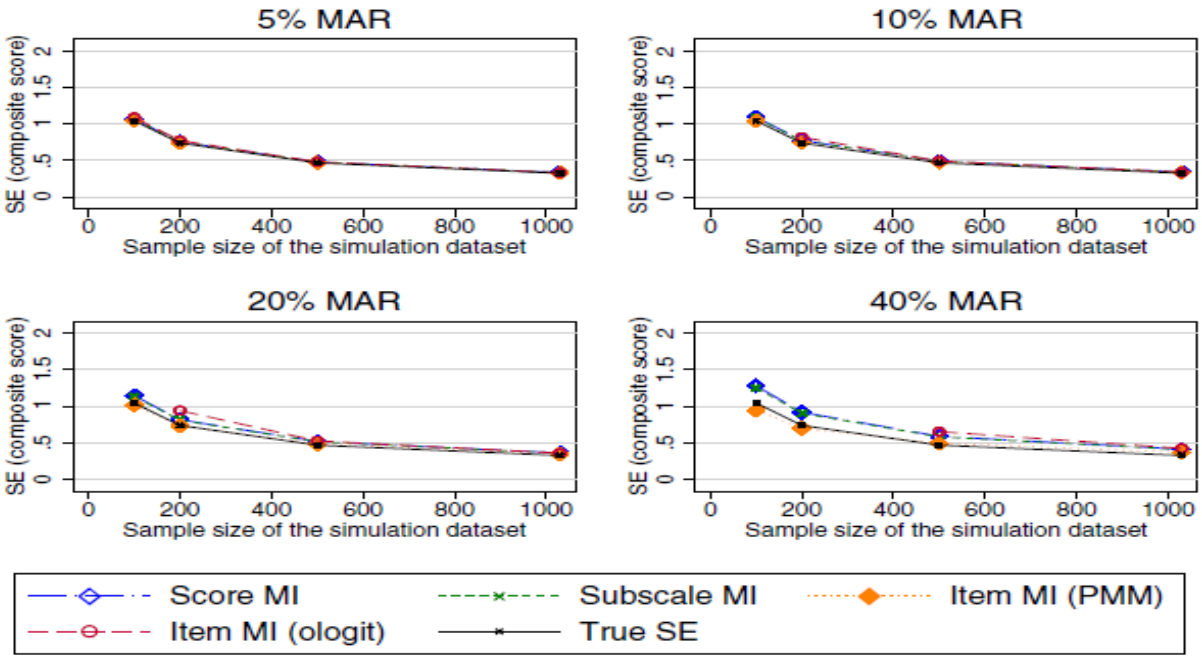


**Fig. 4** SE in the OKS composite score estimates (observed missing data pattern). Abbreviations: MAR – Missing at random; MI – Multiple imputation; PMM – Predicted mean matching; SE – Standard Error

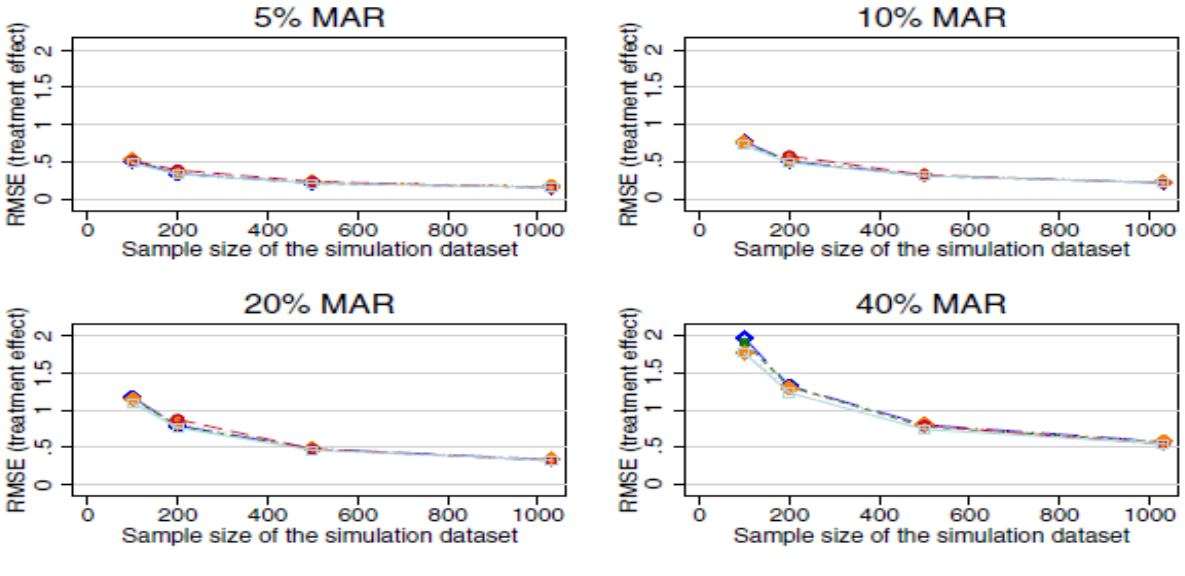


**Fig. 5** RMSE in the treatment effect estimates using the imputed OKS composite scores as the outcome variable in the regression model (observed missing data pattern). Abbreviations: CCA – Complete cases analysis; MAR – Missing at random; MI – Multiple imputation; OKS – Oxford knee score; PMM – Predicted mean matching; RMSE – Root mean square error

**Table 3** Impact of the different analysis approaches on the trial conclusion

| Analysis approach | Treatment effect (95% CI) | Number of participants included |
|---|---|---|
| Complete cases analysis | 0.9 (−2.6, 4.4) | 167 |
| MI at the composite score level | 0.7 (−2.8, 4.2) | 200 |
| MI at the subscale level | 0.7 (− 2.7, 4.1) | 200 |
| MI at the item level (ologit) | 0.9 (−2.5, 4.3) | 200 |
| MI at the item level (PMM) | 0.6 (−2.7, 3.9) | 200 |

# Recommendations

- Imputation at the item/subscale level may provide more precise estimates of treatment effect compared to the imputation at the composite score level or CCA
- Imputation at the item/subscale level is often infeasible and prone to convergence
- Appropriate sensitivity analysis to assess the impact of missing data

**Gianluca Baio, PhD, MSc**
Professor of Statistics and Health Economics
University College London (UCL)

# Fully Bayesian MI as an Alternative

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**Objective**: Combine costs & benefits of a given intervention into a rational scheme for allocating resources, increasingly often under a Bayesian framework

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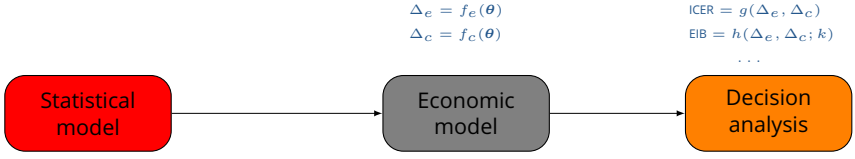


- Estimates relevant **population** parameters $\boldsymbol{\theta}$
- Varies with the type of available data (& statistical approach!)

- Combines the parameters to obtain a population average measure for costs and clinical benefits
- Varies with the type of available data & statistical model used

- Summarises the economic model by computing suitable measures of "cost-effectiveness"
- Dictates the best course of actions, given current evidence
- Standardised process

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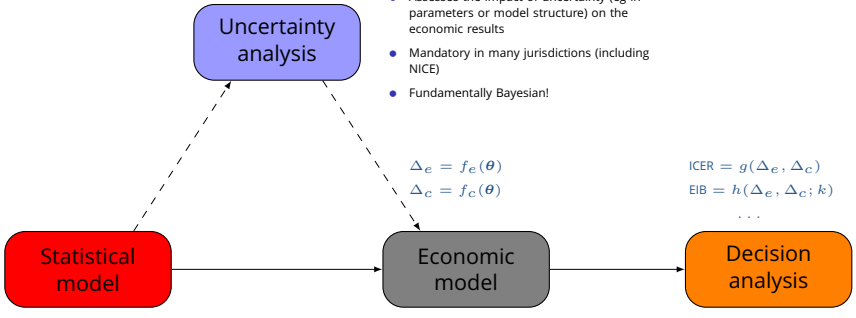

# "Standard" Statistical modelling — Individual level data in HTA

| | | Demographics | | | HRQL data | | | | Resource use data | | | | Clinical outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **ID** | **Trt** | Sex | Age | ... | $u_0$ | $u_1$ | ... | $u_J$ | $c_0$ | $c_1$ | ... | $c_J$ | $y_0$ | $y_1$ | ... | $y_J$ |
| 1 | 1 | M | 23 | ... | 0.32 | 0.66 | ... | 0.44 | 103 | 241 | ... | 80 | $y_{10}$ | $y_{11}$ | ... | $y_{1J}$ |
| 2 | 1 | M | 21 | ... | 0.12 | 0.16 | ... | 0.38 | 1204 | 1808 | ... | 877 | $y_{20}$ | $y_{21}$ | ... | $y_{2J}$ |
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3. Estimate population average cost and effectiveness differentials and use bootstrap to quantify uncertainty

# What's wrong with this?...

- Potential correlation between costs & clinical benefits
  - Strong positive correlation — effective treatments are innovative and result from intensive and lengthy research ⇒ are associated with higher unit costs
  - Negative correlation — more effective treatments may reduce total care pathway costs e.g. by reducing hospitalisations, side effects, etc.
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- ... and of course **Partially Observed** data — **Particularly for small/pilot studies**
  - Can have item and/or unit non-response
  - Missingness may occur in either or both benefits/costs
  - The missingness mechanisms may also be correlated
  - What exactly to adjust for, at baseline — **available vs complete cases**!

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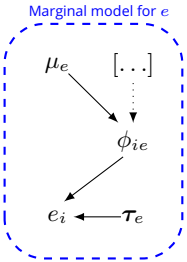


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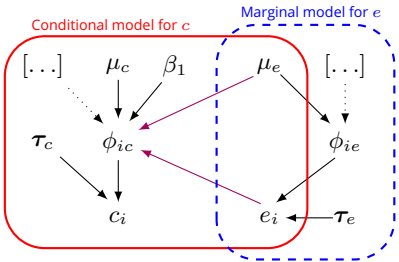


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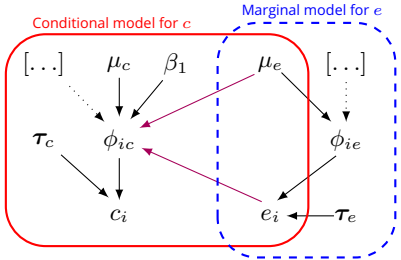


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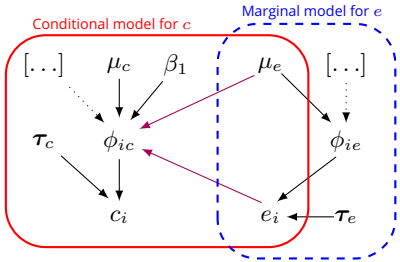


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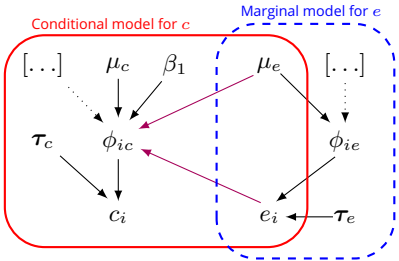


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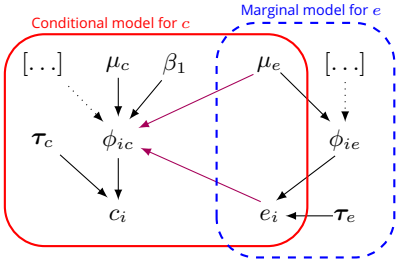


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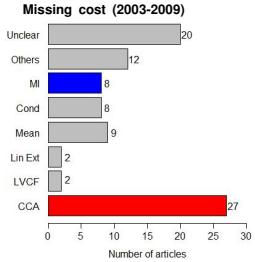
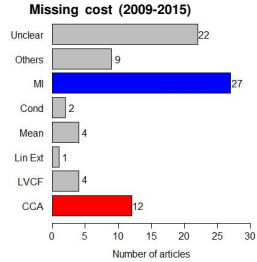
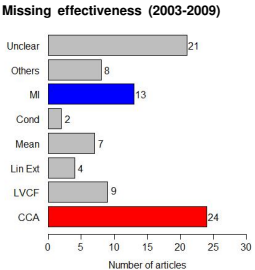
- Combining "modules" and fully characterising uncertainty about deterministic functions of random quantities is relatively straightforward using MCMC
- Prior information can help stabilise inference (especially with sparse data!), eg
  - Cancer patients are unlikely to survive as long as the general population
  - ORs are unlikely to be greater than $\pm 5$

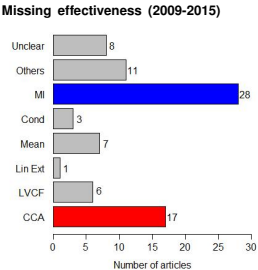
# Known unknowns?...

Gabrio et al. (2017). *PharmacoEconomics Open*, 1(2), 79-97



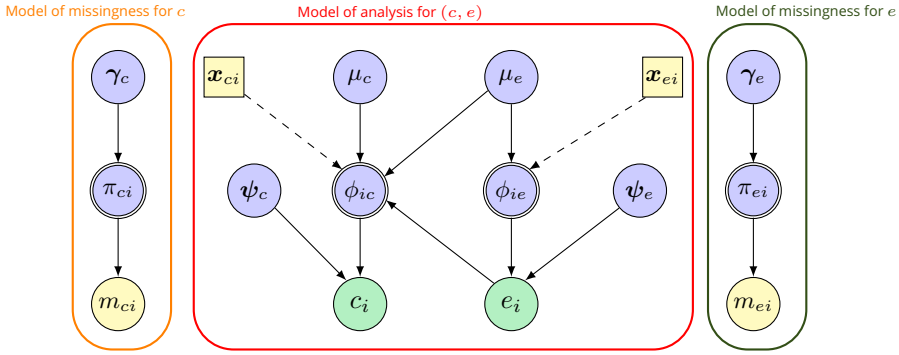



# (Bayesian) Missing data in HTA



MCAR $(e, c)$




- $m_{ei} \sim \text{Bernoulli}(\pi_{ei})$; $\quad \text{logit}(\pi_{ei}) = \gamma_{e0}$
- $m_{ci} \sim \text{Bernoulli}(\pi_{ci})$; $\quad \text{logit}(\pi_{ci}) = \gamma_{c0}$

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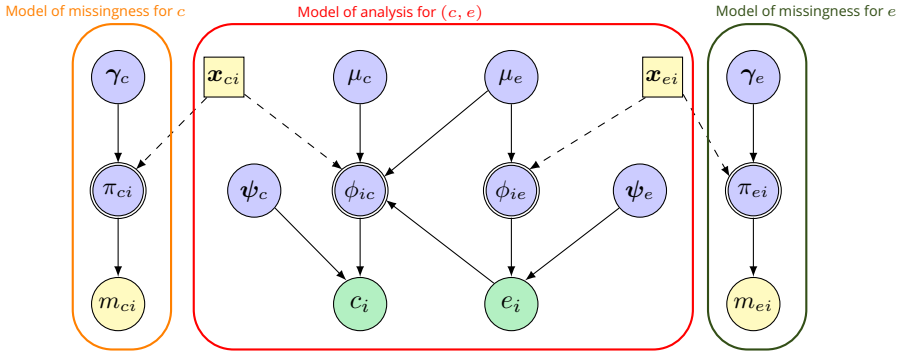


- $m_{ei} \sim \text{Bernoulli}(\pi_{ei})$; $\quad \text{logit}(\pi_{ei}) = \gamma_{e0} + \sum_{k=1}^{K} \gamma_{ek} x_{eik}$
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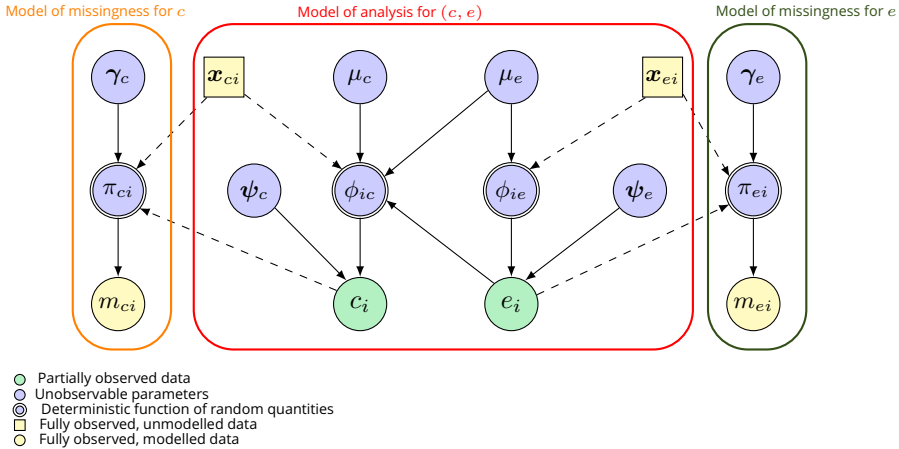


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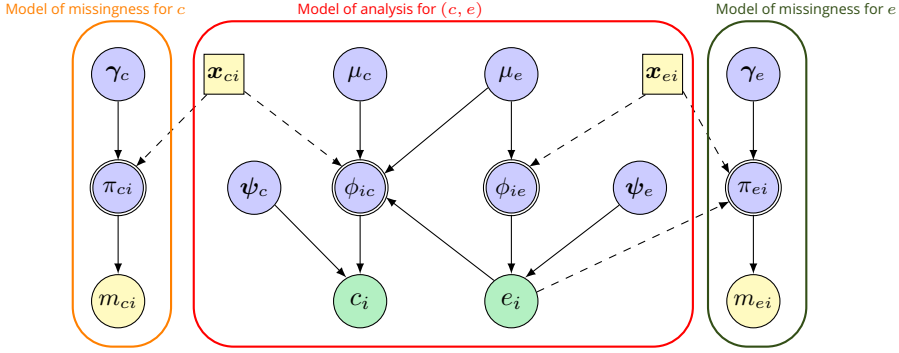
- $m_{ci} \sim \text{Bernoulli}(\pi_{ci})$; $\quad \text{logit}(\pi_{ci}) = \gamma_{c0} + \sum_{h=1}^{H} \gamma_{ch} x_{cih} + \gamma_{cH+1} c_i$

# (Bayesian) Missing data in HTA



MNAR $e$; MAR $c$

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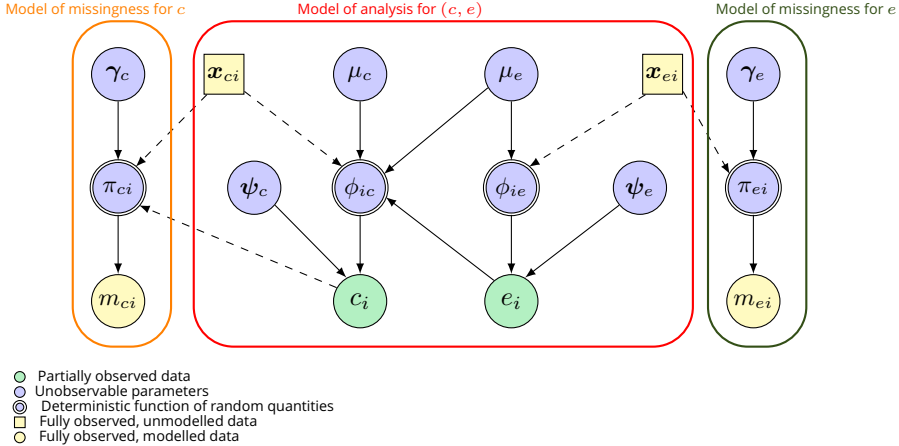
# (Bayesian) Missing data in HTA

**Selection models**

MAR $e$; MNAR $c$

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# Motivating example: MenSS trial

- The MenSS pilot RCT evaluates the cost-effectiveness of a new digital intervention to reduce the incidence of STI in young men with respect to the SOC
  - QALYs calculated from utilities (EQ-5D 3L)
  - Total costs calculated from different components (no baseline)

# Motivating example: MenSS trial

**Partially observed data**

- The MenSS pilot RCT evaluates the cost-effectiveness of a new digital intervention to reduce the incidence of STI in young men with respect to the SOC
  - QALYs calculated from utilities (EQ-5D 3L)
  - Total costs calculated from different components (no baseline)

| Time | Type of outcome | observed (%) | observed (%) |
|---|---|---|---|
| | | Control ($n_1$=75) | Intervention ($n_2$=84) |
| Baseline | utilities | 72 (96%) | 72 (86%) |
| 3 months | utilities and costs | 34 (45%) | 23 (27%) |
| 6 months | utilities and costs | 35 (47%) | 23 (27%) |
| 12 months | utilities and costs | 43 (57%) | 36 (43%) |
| **Complete cases** | utilities and costs | 27 (44%) | 19 (23%) |

# Motivating example: MenSS trial

**Skewness & "structural values"**

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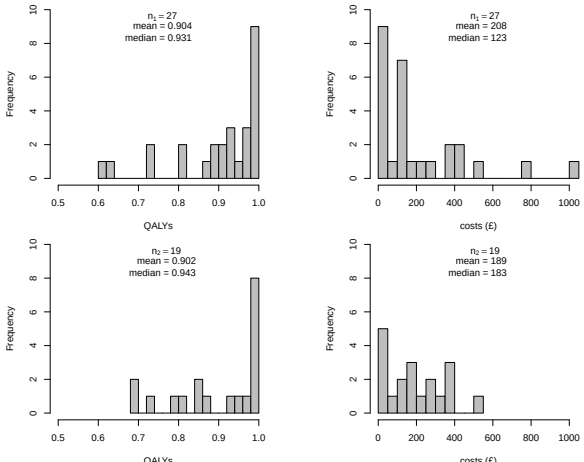
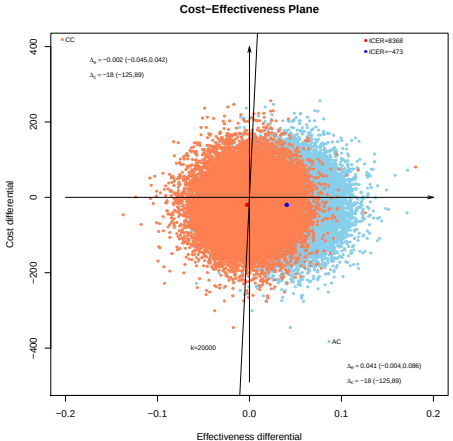
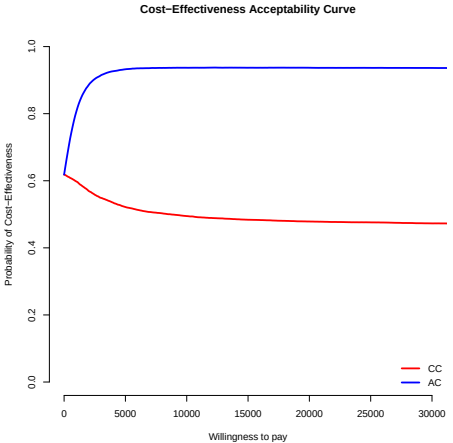


# Cost-effectiveness analysis (1)

## Normal & Independent outcomes



# Modelling

Gabrio et al. (2018). https://arxiv.org/abs/1801.09541 + SiM (in press)

## Bivariate Normal

- Simpler and closer to "standard" frequentist model
- Account for correlation between QALYs and costs

**Conditional model for $c \mid e$**

$$c_{it} \mid e_{it} \sim \text{Normal}(\phi_{cit}, \psi_{ct})$$
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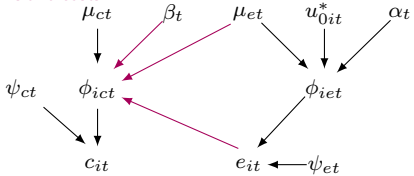


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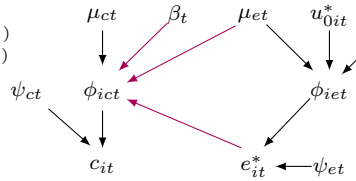


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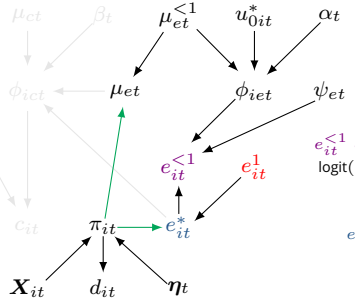


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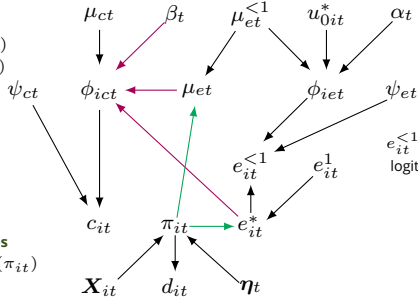


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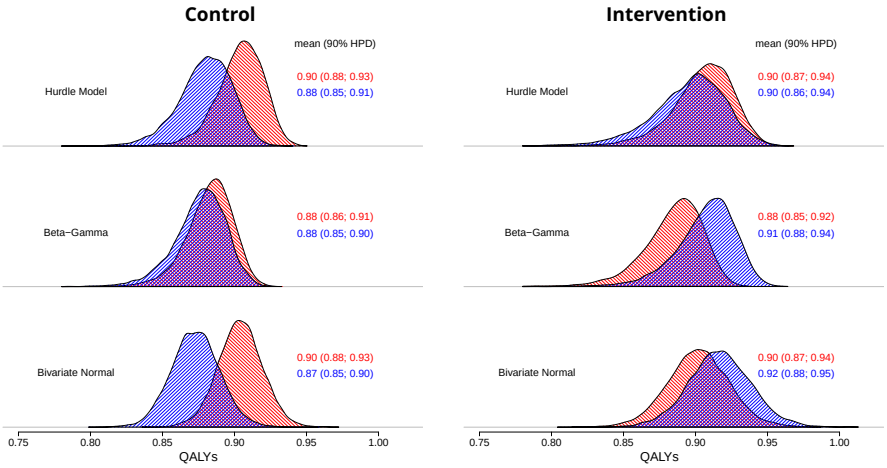
# Results

**Complete only vs all cases**




Complete cases only

All cases (missing at random, MAR)

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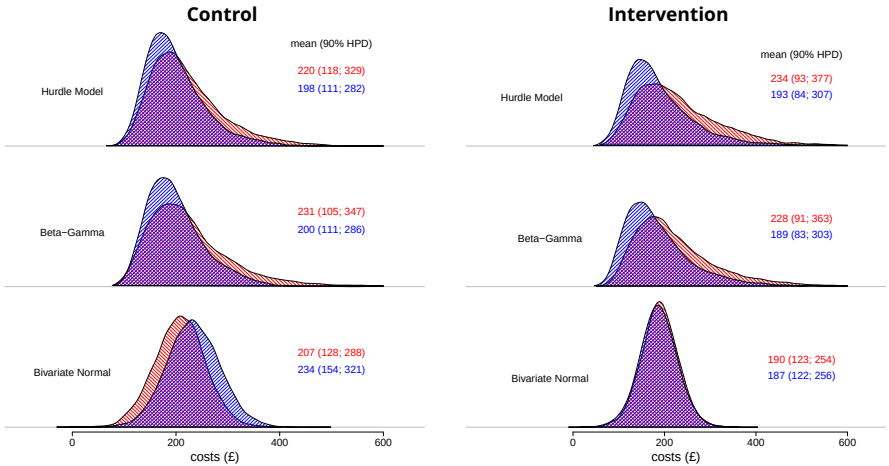


Complete cases only
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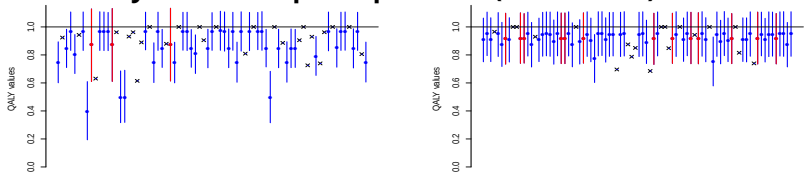
**Bivariate Normal**

# Bayesian multiple imputation (under MAR)




Imputed, observed baseline
Imputed, missing baseline
Observed

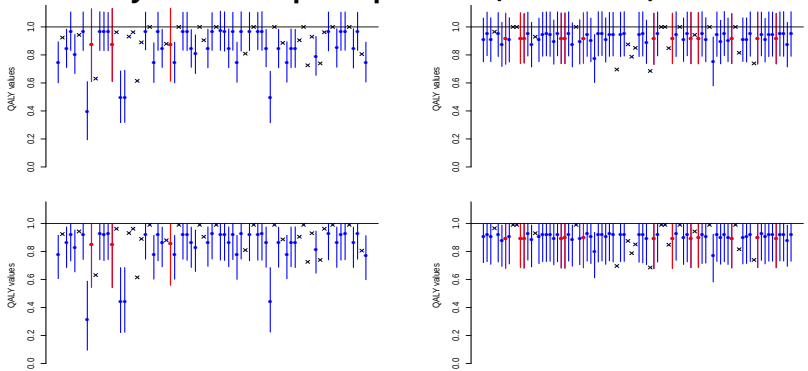
Individuals ($n_1 = 75$)

Individuals ($n_2 = 84$)

# Bayesian multiple imputation (under MAR)

**Bivariate Normal**

**Beta-Gamma**



# Bayesian multiple imputation (under MAR)

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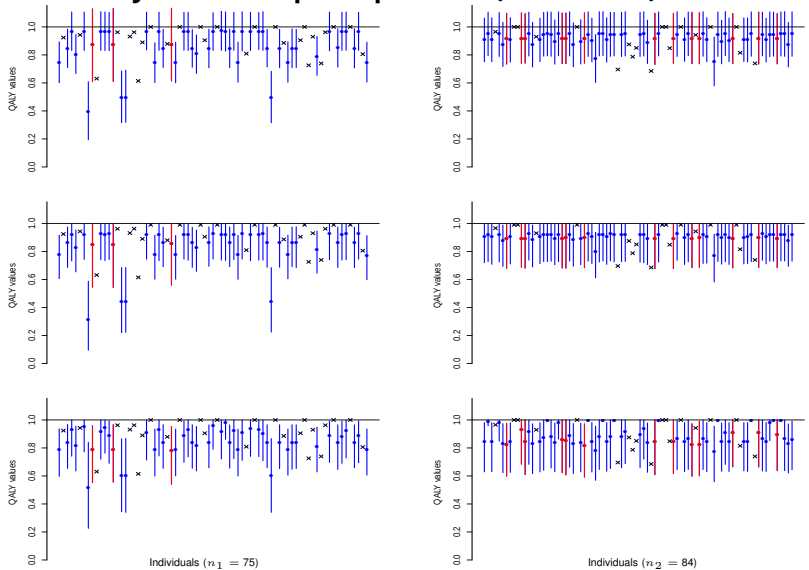
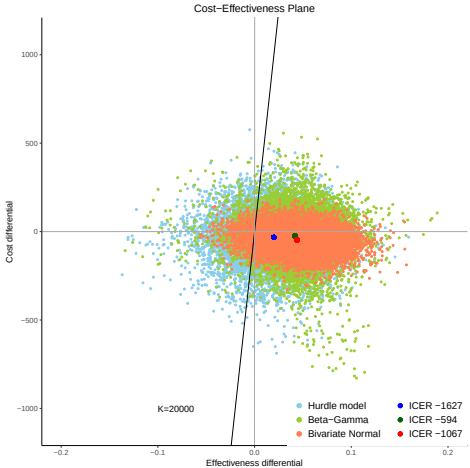
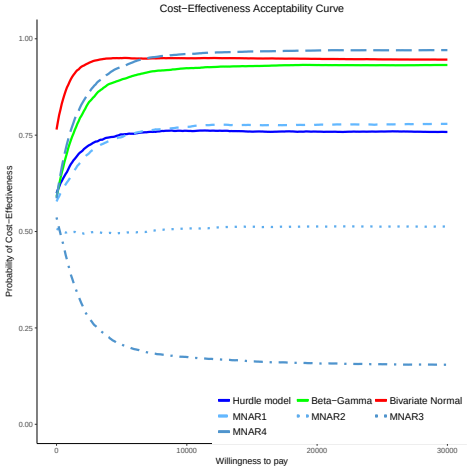


# Cost-effectiveness analysis (2)

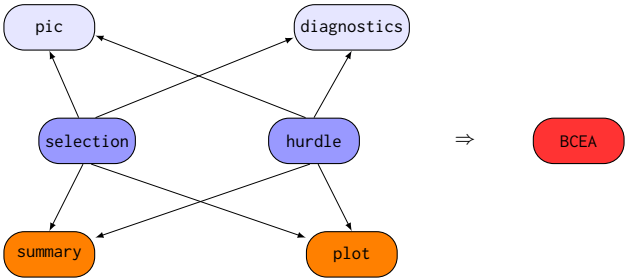



**More complex modelling**



# missingHE: a R package to deal with missing data in HTA

**Objective**: Run a set of complex models to account for different level of complexity & missingness




Gabrio et al. (2018). https://arxiv.org/abs/1801.09541
https://github.com/giabaio/missingHE

# Conclusions

- A full Bayesian approach to handling missing data extends standard “imputation methods”
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  - Correlation between costs & benefits
  - Structural values (eg spikes at 1 for utilities or spikes at 0 for costs)

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- Particularly helpful in cost-effectiveness analysis, to account for
  - Asymmetrical distributions for the main outcomes
  - Correlation between costs & benefits
  - Structural values (eg spikes at 1 for utilities or spikes at 0 for costs)
- Need specialised software + coding skills
  - R package **missingHE** under development to implement a set of general models
  - Preliminary work available at https://github.com/giabaio/missingHE

```
prior = list("mu.prior.e"=mu.prior.e,"delta.prior.e"=delta.prior.e)
model = run_model(data=data,model.eff=e~1,model.cost=c~1,
                  dist_e="norm",dist_c="norm",type="MNAR_eff",stand=FALSE,
                  program="JAGS",forward=FALSE,prob=c(0.05,0.95),n.chains=2,n.iter=20000,
                  n.burnin=floor(20000/2),inits=NULL,n.thin=1,save_model=FALSE,prior=prior
                )
```

  - Eventually, will be able to combine with existing packages (eg **BCEA**: http://www.statistica.it/gianluca/BCEA; https://github.com/giabaio/BCEA) to perform the whole economic analysis

# Thank you!

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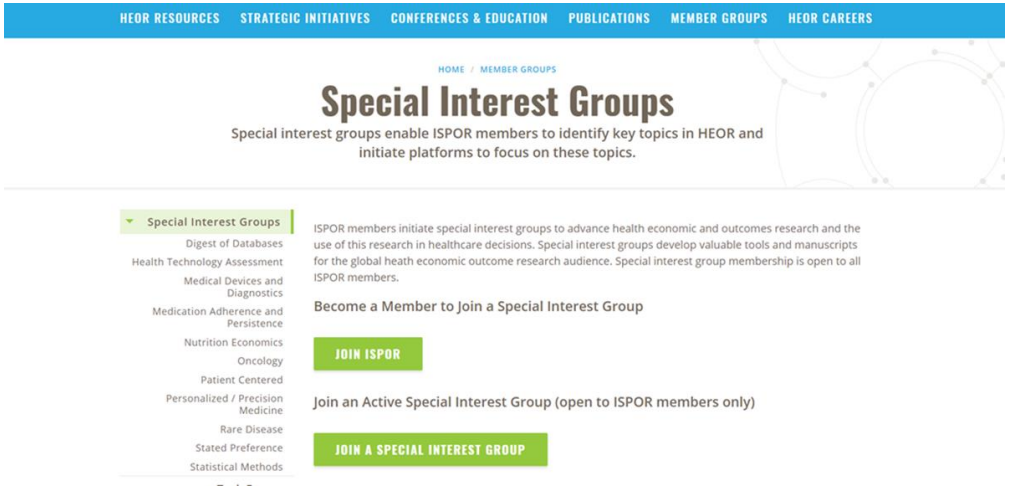


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