Title: Underestimation of Variance of Predicted Mean Health Utilities Derived from Multi-Attribute Utility Instruments: The Use of Multiple Imputation as a Potential Solution.

Abstract: Parameter uncertainty in value sets (of health utilities) of multi-attribute utility-based instruments (MAUIs) has received little attention previously. This false precision leads to underestimation of the uncertainty of the results of cost-effectiveness analyses. This may result in drug funding decisions based on invalid estimates of cost-effectiveness of cancer drugs. In this presentation, we will illustrate the presence and magnitude of this parameter uncertainty by fitting a Bayesian model with random effects for respondents and health states to the data from the original US EQ-5D-3L valuation study, thereby estimating the uncertainty in the EQ-5D-3L scoring algorithm. We will then demonstrate the use of multiple imputation as a method to account for this uncertainty of MAUI scoring algorithms. We will apply these methods to the EQ-5D-3L data from the Commonwealth Fund (CWF) Survey for Sick Adults (n=3958), comparing the standard error of the estimated mean utility in the CWF population using the predictive distribution from the Bayesian mixed effect model (i.e., incorporating parameter uncertainty in the value set) with the standard error of the estimated mean utilities based on multiple imputation and the standard error using the conventional approach of using MAUI (i.e., ignoring uncertainty in the value set). This presentation will allow us to appreciate that ignoring uncertainty of the predicted health utilities derived from MAUIs could lead to substantial underestimation of the variance of mean utilities. The use of multiple imputation method can correct for this underestimation so that the results of cost-effectiveness analyses using MAUIs can report the correct degree of uncertainty.
Underestimation of Variance of Predicted Mean Health Utilities Derived from Multi-Attribute Utility Instruments: The Use of Multiple Imputation as a Potential Solution.

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Hospital of Sick Children,

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Co-Director, Canadian Centre for Applied Research in Cancer Control (ARCC),
Clinical Lead, Provincial Drug Reimbursement Programs, Cancer Care Ontario.
Health utilities

...affect you
...are reported alongside underestimates of uncertainty

We aim to explain:
- why you should care
- where the uncertainty comes from
- what to do about it
Health utilities are used to decide which treatments to reimburse.
QALY = quality-adjusted life year 4

QALYs at time $t = \int_{0}^{t} \text{utility}(s) ds$
Why is this topic important in Oncology? $ $

- Funding of cancer drugs in Canada depends on evaluation of cost-effectiveness (as part of Health Technology Assessment)
- Pan-Canadian Oncology Drug Review (pCODR) at the Canadian Agency of Drug and Technology in Health (CADTH)
- CADTH has recently published an updated guideline for economic evaluation for HTA in Canada (2017) suggesting that the base case should be a probabilistic analysis (not deterministic)
Why is this topic important in Oncology?

• The main outcome of a cost-effectiveness analysis is called incremental cost-effectiveness ratio (ICER)

\[
ICER = \frac{\Delta C}{\Delta E}
\]

• Incremental Cost = \( \Delta C \)
• Incremental Effectiveness = \( \Delta E \)
Why is this topic important in Oncology?

\[ E(\text{ICER}) = E\left(\frac{\Delta C}{\Delta E}\right) \neq \frac{E(\Delta C)}{E(\Delta E)} \]

Therefore, probabilistic analysis is essential to fully account for the joint distributions of all the parameters in the model to estimate an unbiased ICER and its distribution (degree of uncertainty).
Why is this topic important in Oncology? 

\[ ICER = \frac{\Delta C}{\Delta E} \]

- In Oncology cost-effectiveness analysis, 
  \[ \Delta E = \Delta QALY = \Delta (utility \times \text{survival}) \]

- Hence, the importance of capturing the uncertainty of utility adequately
- Otherwise, drug funding decision may be based on invalid estimate of the distribution of ICER
Why does uncertainty matter? $

• Reimbursement decision making
  – Evidence based
  – *Estimates* of incremental cost and utility (ICERs, etc.)
  – Quality of estimates matters
    • ICER of $40,000 per QALY with 95% CI ($5,000 to $300,000)
    • ICER of $40,000 per QALY with 95% CI ($35,000 to $50,000)
Health Utility and QALYs

Figure: Determining Quality-Adjusted Survival—Length of life (time) is plotted against quality of life (utility). The area under the curve represents quality-adjusted survival measured in quality-adjusted life years (QALYs).
Direct Measures'

(a) Time Trade-Off (TTO)

(b) Standard Gamble (SG)
MAUI – Example EQ-5D %

Figure 1. EQ-5D example from http://diabetesclinicevaluation.weebly.com/uploads/9/5/6/7/9567609/6029985.jpg?633
### Measuring Health Utilities *

<table>
<thead>
<tr>
<th>Direct Measures</th>
<th>Indirect Measures</th>
<th>Mapping Algorithms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Time Trade-off</td>
<td>• Multi-Attribute Utility Index (MAUI)</td>
<td>• Many</td>
</tr>
<tr>
<td>• Standard Gamble</td>
<td>• EQ-5D</td>
<td>• Developed using health-related quality of life measures (HRQOL)</td>
</tr>
<tr>
<td></td>
<td>• SF-6D</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• HUI3</td>
<td></td>
</tr>
</tbody>
</table>

Country-specific functional form of scoring algorithm *
US EQ-5D scoring algorithm # (established valuation study) #

For subject $i$ valuing state $j$: 

$E(TTO_{ij}) = \mu_j = 1 - \text{disutility}_j$

$\text{disutility}_j = X_j \beta$

$X_j = (MO_{2j}, MO_{3j}, SC_{2j}, SC_{3j}, UA_{2j}, UA_{3j}, PD_{2j}, PD_{3j}, AD_{2j}, AD_{3j}, D_1, I_{2j}^2, I_{3j}, I_{3j}^2),$

$MO_{2j} = 1$ if state $j$ has mobility at level 2, 0 o/w
$MO_{3j} = 1$ if state $j$ has mobility at level 3, 0 o/w

$D_1 =$ # of movements away from full health beyond the first,
$I_{2j} = $ # of dimensions at level 2 beyond the first,
$I_{3j} = $ # of dimensions at level 3 beyond the first.
US EQ-5D-3L: Health state (1,2,3,2,1) 

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff.</th>
</tr>
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<tbody>
<tr>
<td>M2</td>
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</tr>
<tr>
<td>M3</td>
<td>0.558</td>
</tr>
<tr>
<td>S2</td>
<td>0.175</td>
</tr>
<tr>
<td>S3</td>
<td>0.471</td>
</tr>
<tr>
<td>U2</td>
<td>0.140</td>
</tr>
<tr>
<td>U3</td>
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<td>P2</td>
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<td>P3</td>
<td>0.537</td>
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</tr>
<tr>
<td>A3</td>
<td>0.450</td>
</tr>
<tr>
<td>D1</td>
<td>-0.140</td>
</tr>
<tr>
<td>I2-squared</td>
<td>0.011</td>
</tr>
<tr>
<td>I3</td>
<td>-0.122</td>
</tr>
<tr>
<td>I3-squared</td>
<td>-0.015</td>
</tr>
</tbody>
</table>

Utility(1,2,3,2,1) = 1 - (0.175 + 0.374 + 0.173 - 2*0.140 + 0.011) = 0.547
What’s the issue?

• Scoring algorithms yield predictions of population mean utility
• Predictions are subject to uncertainty
• MAUIs elicit utilities subject to uncertainty
• What impact on uncertainty of estimates of
  – Population mean utility
  – Incremental mean utility?
Predictions.

- Regression modelling
- Uncertainty in line itself
- Points do not lie perfectly on the line.

\[ E(TTO_{ij}) = \mu_j = 1 - X_j \beta \]
EQ-5D-3L US valuation study

- 3773 respondents
- Each valued 10 health states using TTO
- 42 health states valued in total
- Modelled mean utility for each health state as a function of health state attributes
- Predicted mean utilities for all 243 health states
- Observed MSE vs theoretical MSE assuming no model mis-fit
- Bayesian analysis to yield \textit{predictive distribution} for each mean utility
Quantifying prediction precision *

- Compute out-of-sample prediction errors
- Omit health state j from analysis and compute expected value of observed minus predicted mean

\[
Y_{ij} = 1 - X_j \beta + b_i + \varepsilon_{ij} \quad \text{with } b_i \sim N(0, \sigma_b^2), \ \varepsilon_{ij} \sim N(0, \sigma_e^2),
\]

\[
E(\bar{Y}_j - 1 + X_j \hat{\beta}_{(j)})^2
= E(\bar{Y}_j - \mu_j)^2 + E(X_j \beta - X_j \hat{\beta}_{(j)})^2 + 2 \text{cov}(X_j \hat{\beta}_{(j)}, \bar{Y}_j)
= \text{var}(\bar{Y}_j) + X_j \ \text{var}(\hat{\beta}_{(j)}) X_j' + 2 \text{cov}(X_j \hat{\beta}_{(j)}, \bar{Y}_j)
\]
We see larger MSEs than we should

\[
E(\bar{Y}_j - 1 + X_j\hat{\beta}_{(i)})^2 = E(\bar{Y}_j - \mu_j)^2 + E(X_j\beta - X_j\hat{\beta}_{(i)})^2 + 2\text{cov}(X_j\hat{\beta}_{(i)}, \bar{Y}_j) \\
= \text{var}(\bar{Y}_j) + X_j\text{var}(\hat{\beta}_{(i)})X_j' + 2\text{cov}(X_j\hat{\beta}_{(i)}, \bar{Y}_j)
\]

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<thead>
<tr>
<th>Source</th>
<th>Contribution</th>
<th>Cumulative sum</th>
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</thead>
<tbody>
<tr>
<td>Sampling variance in observed means</td>
<td>0.00018</td>
<td>0.00018</td>
</tr>
<tr>
<td>Uncertainty in estimated regression coefficients</td>
<td>0.00011</td>
<td>0.00029</td>
</tr>
<tr>
<td>Covariance between observed &amp; fitted mean</td>
<td>-0.0000006</td>
<td>0.00029</td>
</tr>
<tr>
<td>Observed MSE on cross-validation</td>
<td>0.00178</td>
<td>0.00178</td>
</tr>
<tr>
<td>Uncertainty due to model mis-specification</td>
<td>0.00178-0.00029</td>
<td>0.00149</td>
</tr>
</tbody>
</table>
Regression Model with model mis-fit

\[
\mu_j = 1 - X_j \beta + \delta_j, \quad \delta_j \sim N(0, \sigma^2_d)
\]

\[
Y_{ij} = \mu_j + b_i + \varepsilon_{ij} \quad \text{with} \quad b_i \sim N(0, \sigma^2_b), \quad \varepsilon_{ij} \sim N(0, \sigma^2_e),
\]

Can think of \(\delta\) as
- model mis-fit term with a Gaussian prior
- or can conceptualise as a random effect

Vague priors for \(\delta, \beta, \sigma\)

Get predictive distribution of \(\mu_j\)
How much uncertainty?

Black dots – predicted means
x’s – observed means

Black lines – 95% CI ignoring model mis-fit
Grey lines – 95% CI accounting for model mis-fit
How much uncertainty? $

Health states not included in valuation study

• Mean 95% CI width: 0.152
• Range in 95% CI width: 0.142-0.169

Minimum important difference for the EQ-5D-3L $

• 0.03 to 0.08
Does it matter? %

• Level of uncertainty may be important
• MAUIs used in HTA to calculate
  – Population mean utility
  – Incremental QALYs (difference in QALYs between groups)
• Use simulation to estimate impact of uncertainty in the scoring system on uncertainty in (incremental) mean utilities.
Population mean utility

• Each respondent fills out the EQ-5D-3L
• Scoring algorithm -> utility for each respondent
• Target of inference: population mean utility
• Sources of uncertainty
  – Sampling variation in health states
  – Uncertainty in scoring algorithm
• Sample of 500 adults from the US general population
• Take random subsamples of varying sizes
Incremental mean utility

- Simulate data from an RCT
  - Simulate health state distributions
  - Simulate health states for each person in each arm of the trial
  - Scoring algorithm -> utilities
  - Mean utility per arm
  - Difference -> incremental mean utility
For an arbitrarily large study, accounting for uncertainty in the scoring algorithm.
Findings so far…

• Uncertainty in scoring algorithm is substantial
• Should be accounted for
  – Bayesian methods
  – Multiple imputation (Dr Kelvin Chan)
• Problem not unique to the EQ-5D
  – E.g. SF-6D utilities estimated subject to std error of 0.06
• Current practice gives decision makers a false level of certainty.
What is the problem?

- Health utilities in the value sets of MAUI are subject to uncertainty
  - E.g. 95% CI prediction error
    - $\pm 0.0754$ for EQ-5D
    - $\pm 0.1655$ for SF-6D

- Minimal clinically important differences
  - $0.05 - 0.08$ for EQ-5D
  - $0.01 - 0.09$ for SF-6D


What is the problem?

\[ \mu_j = 1 - X_j \beta + \delta_j \]

Traditionally, utilities from MAUI were treated as known with certainty (rather than estimated with uncertainty)

Ignore \( \delta_j \)

\[ \hat{\mu}_j = 1 - X_j \beta \]

\(^4\text{Pullenayegum EM, Chan KKW, Feng X. EQ-5D health utilities are estimated subject to considerable uncertainty. MDM 2015.}\)
What is the problem?

• No method to account for variance of the estimated predicted mean health state utilities from MAUI
  • E.g. subjects with the same health states will always “map” to the same health utility without variation

• Cost-utility analyses based on MAUI do not capture parameter uncertainty in quality-adjusted life years
1. Full Bayesian analysis
   • Using posterior predictive distributions of health states using original study data\(^1\)

Need to specify a likelihood for the data, and acknowledge the possibility of model misspecification:

\[
\mu_j = 1 - X_j \beta + \delta_j
\]

If no misspecification \(\delta_j = 0\) for all \(j\)

---

\(^1\)Pullenayegum EM, Chan KKW, Feng X. EQ-5D health utilities are estimated subject to considerable uncertainty. MDM 2015.
Bayesian Analysis

Utility

- Posterior
- Likelihood
- Prior
Bayesian Analysis

• Challenges:
  • Requires implementation by the original authors
  • Lack of raw data from valuation studies

1Pullenayegum EM, Chan KKW, Feng X. EQ-5D health utilities are estimated subject to considerable uncertainty. MDM 2015.
Multiple Imputation

• Three phases:

1. Missing data are filled in $m$ times to generate $m$ complete data sets

2. The $m$ complete data sets are analyzed by using standard procedures

3. The results from the $m$ complete data sets are combined for the inference
Multiple Imputation

Incomplete data

Set 1
<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
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</thead>
<tbody>
<tr>
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<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>6</td>
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Set 2
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Set 3
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<th>B</th>
<th>C</th>
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<tr>
<td>4</td>
<td>5</td>
<td>2</td>
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</tbody>
</table>

Imputed data

Separate analysis

Results set 1

Results set 2

Results set 3

Pooled result

Combined results of sets 1 - 3 (Rubin’s rule)

Separate analysis

Multiple Imputation
Solutions

Multiple imputation

- Approximation to Bayesian treatment of parameter uncertainty, used to handle missing data\textsuperscript{2,3}.
  - E.g. true mean utilities of each health state.

- Replaces missing value with a set of plausible values that represent the uncertainty about the right value to impute.

\textsuperscript{2}Rubin DB. Multiple imputation for non-response in surveys. John Wiley & Sons; 1987.
<table>
<thead>
<tr>
<th>EQ-5D-3L</th>
<th>Health States (HS)</th>
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<tr>
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<td>3,3,3,3,2</td>
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<tr>
<td>3,3,3,3,3</td>
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</table>
100 points randomly selected from each health state to generate 100 imputed datasets

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility</th>
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<tbody>
<tr>
<td>2</td>
<td>$x_{1,2}$</td>
</tr>
<tr>
<td>3</td>
<td>$x_{1,3}$</td>
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<td>$x_{1,4}$</td>
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<td>$x_{1,243}$</td>
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<table>
<thead>
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<tr>
<td>2</td>
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<table>
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A sample of 5 subjects

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<th>Utility</th>
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<td>$X_{1,3}$</td>
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<td>$X_{1,11}$</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>$X_{1,125}$</td>
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<td>4</td>
<td>200</td>
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<tr>
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Generate 100 imputed datasets

Set 1

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<tbody>
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Set 2

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Set 3

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<th>Utility</th>
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<tr>
<td>5</td>
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<td>$X_{100,243}$</td>
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</tbody>
</table>

Set 100

Separate analysis

Set 1 Mean utility & variance

Set 2 Mean utility & variance

Set 3 Mean utility & variance

Set 100 Mean utility & variance

Total mean utility and variance (Rubin’s Rule)

Pooled result
Validation (Aim)

• Using the US EQ-5D-3L valuation study,

• Demonstrate that multiple imputation can correct underestimation of variance of mean health utilities
Methods: Full Bayesian Analysis

- Derivation set: N = 3,773 (US EQ-5D-3L)
- Application set: N = 3,958 (CWF dataset)
- Derivation set used D1 model, which was fitted to Bayesian mixed effect model
  - Obtained posterior predictive distribution of the mean utility attached to each health state
  - Applied to application set to compute mean and variance
Approach

1. Fit a full Bayesian model

\[ \mu_j = 1 - X_j\beta + \delta_j \]

- \( \mu_j \): health utility of the \( j \)th health state
- \( X_j\beta \): linear predictor of the MAUI of the \( j \)th health state
- \( \delta_j \): deviation of predicted health utility from the true utility

2. Use the joint predictive distribution to implement multiple imputation
• Simulated US EQ-5D data to examine the 95% CI coverage of health utilities from multiple imputation

<table>
<thead>
<tr>
<th></th>
<th>Using Covariance Matrix of US D1 Regression Model</th>
<th>Random sampling of joint predictive distributions (MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Health States that have coverage &gt;95%</td>
<td>2 out of 42</td>
<td>38 out of 42</td>
</tr>
<tr>
<td>Percentage of coverage</td>
<td>40%</td>
<td>98%</td>
</tr>
</tbody>
</table>
Methods to illustrate that multiple imputation can be used to correct for the underestimation of variance of mean health utilities of the sample.
Results

Comparisons of the sample mean and sample standard error of the mean health utility of the application set (N = 3958) based on (i) the regression coefficients (i.e. scoring algorithm), (ii) the full Bayesian model's posterior predictive distribution and multiple imputation

<table>
<thead>
<tr>
<th></th>
<th>Traditional Method (based on coefficients)</th>
<th>Multiple Imputation</th>
<th>Full Bayesian Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.827</td>
<td>0.828</td>
<td>0.827</td>
</tr>
<tr>
<td>Variance</td>
<td>$7.96 \times 10^{-6}$</td>
<td>$1.28 \times 10^{-4}$</td>
<td>$1.27 \times 10^{-4}$</td>
</tr>
<tr>
<td>SE</td>
<td>$2.82 \times 10^{-3}$</td>
<td>$1.13 \times 10^{-2}$</td>
<td>$1.12 \times 10^{-2}$</td>
</tr>
</tbody>
</table>
95% of confidence intervals (CI)/credible regions (CR) of sample mean utility of the application set
• Multiple imputation provides “middle ground”
  • Researchers do not have to learn Bayesian methods
  • Variance and standard error reflect appropriate degree of parameter uncertainty
  • Applicable to a wide variety of analyses (e.g. regressions) where traditional MI is applicable.
Limitations

- Need original publishers of MAUI studies to create the imputed datasets to make it publicly available to apply this imputation method
Conclusions

MI is a potential method to account for the underestimation of variance of predicted health utilities
Current work

• Improving precision based on existing data
  – Use posterior distribution of $\delta$
  – Model correlation among $\delta$

• Improving precision based on better designs
  – How many health states to value?
  – Quantify MSE as a function health state selection & SS
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Extra Slides
Multiple Imputation

MCMC method:

The imputation I-step: draw values of $Y_{i\text{ (mis)}}$ from a conditional distribution of $Y_{i\text{ (mis)}}$ given $Y_{i\text{ (obs)}}$

The posterior P-step: simulates the posterior population mean vector and covariance matrix from the complete sample estimates
Multiple Imputation

• Three phases:

1. Missing data are filled in \( m \) times to generate \( m \) complete data sets

2. The \( m \) complete data sets are analyzed by using standard procedures

3. The results from the \( m \) complete data sets are combined for the inference
Multiple Imputation

With \( m \) imputations, you can compute \( m \) different sets of the point and variance estimates for a parameter \( Q \). Let \( \hat{Q}_i \) and \( \hat{U}_i \) be the point and variance estimates from the \( i \)th imputed data set, \( i=1, 2, ..., m \). Then the point estimate for \( Q \) from multiple imputations is the average of the \( m \) complete-data estimates:

\[
\overline{Q} = \frac{1}{m} \sum_{i=1}^{m} \hat{Q}_i
\]

Let \( \overline{U} \) be the within-imputation variance, which is the average of the \( m \) complete-data estimates

\[
\overline{U} = \frac{1}{m} \sum_{i=1}^{m} \hat{U}_i
\]

And \( B \) be the between-imputation variance

\[
B = \frac{1}{m-1} \sum_{i=1}^{m} (\hat{Q}_i - \overline{Q})^2
\]
Multiple Imputation

The total variance is:

\[ T = \bar{U} + (1 + \frac{1}{m})B \]
Multiple imputation

- Multiple imputation with Monte Carlo Markov chain models
  - Performed using derivation set
  - Randomly drawn multiple imputed sets applied to application dataset

- Mean, variance and standard error across imputed sets calculated using Rubin’s rule\textsuperscript{10}

\textsuperscript{10}Rubin DB. Multiple imputation for non-response in surveys. John Wiley & Sons; 1987.
Bayesian mixed effect model

- Take posterior predictive joint distributions of the mean utility to
  - Capture parameter uncertainty
  - Perform multiple imputations (imputed sets drawn randomly from the Gibbs sampler)