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MULTIPLE IMPUTATION FOR ESTIMATING UNIT COSTS IN MULTICENTRE ECONOMIC EVALUATIONS

*Richard Grieve[1], John Cairns[1] and Simon Thompson[2]

[1]Health Services Research Unit, London School of Hygiene and Tropical Medicine
[2]MRC Biostatistics Unit, Cambridge
*Corresponding author (richard.grieve@lshtm.ac.uk)

Abstract

In multicentre cost-effectiveness analysis (CEA) the analyst must decide how to measure and analyse unit costs. For example, CEA may use the mean unit cost from a national database (e.g. NHS reference costs) or from a subsample of study centres. Neither approach recognises that unit costs vary across centres, or that unit costs are unavailable in some centres. This paper proposes the use of multiple imputation (MI), an approach that can predict unit costs in each centre, whilst recognising the statistical uncertainty surrounding this imputation.

We illustrate MI using as a case study a CEA, based on a multicentre RCT (1014 cases, 60 centres) that evaluates whether withdrawing pulmonary artery catheters from routine use in critical care is cost-effective. We compare the approach taken in the original study that used mean unit costs from NHS reference costs, with an approach that derives unit costs from a MI model. This model uses information on average casemix, centre characteristics and reference costs to impute centre-specific unit costs. A multilevel model (MLM) then estimates cost-effectiveness based on MI unit costs compared to using mean unit costs from reference costs. The results show that while the overall estimate of cost-effectiveness was similar across approaches, for some centres cost-effectiveness differed according to whether MI or reference costs were used. The MLM showed that using reference costs underestimated the heterogeneity in incremental cost-effectiveness across the centres.

The paper concludes that using average unit costs in multicentre economic evaluations can lead to biased estimates and inappropriate inferences about cost-effectiveness at a centre-level. MI makes maximum use of the data available, and leads to more appropriate inferences.

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Introduction

Cost-effectiveness analyses (CEA) commonly use data collected alongside multicentre RCTs. A recent advance in the analysis of multicentre CEA is the use of multilevel models (MLMs) (Manca et al. 2005; Willan et al. 2005; Grieve et al. 2007). MLMs recognise clustering in the resource use and outcome data amongst patients recruited from the same centre; they therefore can allow correct inferences to be made (Goldstein 1995). However, methodological development in CEA has not considered unit cost variation across centres. Instead, multicentre CEA have tended to rely on average unit costs, either from unit costs specifically measured for the CEA in a subsample of centres (Willan et al. 2005), or from aggregated databases such as NHS reference costs (e.g. Stevens et al. 2005).

This approach of using average unit costs across treatment centres is not supported by economic theory. Cost function theory suggests that treatment centres adjust resource use according to local relative factor prices (Raikou et al. 2000). Applying average unit costs to each centre's resource use may therefore overstate total costs. Perhaps more importantly, the incremental cost of a particular intervention may vary according to the number and type of centres included in the unit costing (Goree et al. 1999). Policy-makers may make incorrect decisions if they rely on studies estimating unit costs in a small subsample of centres (Goree et al. 1999).

The potential gains from using centre-specific unit costs may not be easily achieved. The research costs of acquiring specific unit costs in each centre may be prohibitive, and national databases of unit costs may not have complete information for each centre. Previous studies have proposed the use of imputation methods to deal with incomplete unit cost data (Schulman et al. 1998, Glick et al. 2002). However, these studies have failed to recognise the uncertainty that surrounds this imputation process. One approach that recognises this statistical uncertainty, is multiple imputation (MI) (Rubin 1987). While MI has been applied for missing resource use data (Briggs et al. 2003), it has not previously been used to impute unit costs.

The aim of this paper is to compare MI of unit costs with a standard method, where average unit costs are taken from the NHS reference cost database. The methods are illustrated using a previously published CEA (Stevens et al. 2005).

Methods

Section 1 describes as a motivating example, a multicentre CEA faced with the issue of which method to use for estimating unit costs. Section 2 highlights different approaches for estimating unit costs. Section 3 explains how MI was implemented in a multicentre CEA. Section 4 describes how MLMs were combined with MI to analyse incremental cost and cost-effectiveness.

Section 1: Motivating example

The central methodological concern in this paper is which approach to take to unit costing in a multicentre CEA. This issue is considered with reference to a multicentre CEA that has characteristics of multicentre CEA more generally. This CEA (PAC-Man) evaluates the management of critically ill patients with a monitoring device, Pulmonary Artery Catheter (PAC) versus an alternative of not using a Pulmonary Artery Catheter (No PAC) (Stevens et al. 2005). The CEA was based on a multicentre RCT that randomised 1014 cases in 60 NHS trusts in the UK to receive either 'PAC' or 'no PAC'. As PACs were routinely used in the UK for patients in intensive care, the CEA described the 'No PAC' group as having 'the intervention'. The study found that there were small gains in mortality and hence QALYs (average gain of 0.12) associated with the intervention at, on average a small positive incremental cost (£599). The CEA reported that the probability that the intervention was cost-effective exceeded 0.5 at realistic thresholds for the ceiling ratio (£20,000-£30,000 per QALY).

An important, general methodological issue raised by this case study is how to estimate unit costs. In this study the only resource use data collected were the length of hospital stay, by ward type (ICU or General Medical). The CEA attempted to collect the key unit costs (cost per day in ICU) in each centre but only 30 out of 60 Trusts returned the required information. The original CEA used the mean unit costs from NHS reference costs (£1,292 per ICU bedday; 2002-3 prices). We now consider alternative approaches.

Information available for estimating unit costs

Relevant information for estimating unit costs is summarised in Box 1. Study-specific unit costs (UC_1) were available in 30 out of the 60 centres in the CEA. Reference costs (UC_2) were available for 46 out of the 60 centres in the CEA, and in 23 of those 30 centres where study-

specific unit costs were available. Centre-level covariates may prove useful for predicting unit costs in those centres where unit cost data are missing. Information was available on average case mix in each ICU, unit size, and teaching hospital status from the Intensive Care National Audit (ICNARC) Case-Mix Programme dataset. This dataset was 'external' to the CEA but includes data from a total of over 150 ICUs in the UK including 45 of the centres in the PAC-Man CEA.

As the grid below demonstrates the patterns of missingness in the information available for estimating unit costs were complex (Box 1). Complete information on each of the variables of interest was only available in 18 centres, the only covariate available in all 60 centres was teaching hospital status. While the pattern of missing data is particular to this study, the notion that these groups of variables are missing for any given multicentre CEA applies more generally.

Box 1: Information available for estimating unit costs in PAC-Man CEA

	Study unit costs	Reference costs	Casemix	Unit size	Teaching Hospital
Notation	UC_{1k}	UC_{2k}	X_{1k}	x_{2k}	x_{3k}
Source	PAC-Man CEA	DoH	ICNARC	ICNARC	DoH/ICNARC
Centre (k)					
1-18	+	+	+	+	+
19-23	+	+		+	+
24-29	+		+	+	+
30	+				+
31-46		+	+	+	+
47-53		+			+
54-58			+	+	+
59-60					+
n	30	46	45	45	60

data available is denoted by '+';

Section 2: Approaches for estimating unit costs in multicentre CEA

Using the unconditional mean from study-specific unit costs or reference costs

Faced with this information, the analyst may choose to estimate average unit costs using data from either study-specific unit costs (UC_{1k}) or from reference costs (UC_{2k}). However, applying the average unit cost across all centres in the study has several potential problems. Firstly, this approach only gives an unbiased estimate of unit costs if it is assumed that unit costs are 'missing completely at random' (MCAR). This assumption would be tenable if, for example UC_1 were measured in centres sampled at random. If, as is more common, centres were chosen or self-

selected according to particular characteristics, for example geographical location, then the data are not MCAR and using the unconditional mean gives a biased estimate of the unit cost.

A second problem is that simply using the mean unit cost (either from study specific or reference costs) ignores any uncertainty in the estimation process, and assumes that the average unit cost is known with certainty. By ignoring the uncertainty in the estimation of unit costs, this approach may underestimate the variance surrounding incremental cost-effectiveness. Thirdly, this approach fails to make full use of the information available. So, if for example, the analysis relies solely on unit costs estimated in a subsample of centres, it ignores information from reference costs that are available for a broader range of centres. Finally, cost function theory would suggest that if health care firms were attempting to achieve economic efficiency then they would adjust their relative resource use according to relative local factor prices (Heathfield and Vibe 1981). While it might be assumed that this relationship does not hold in the NHS, if centres do adjust resource volumes according to local prices, using average unit costs will lead to biased estimates of cost-effectiveness at a local level.

Conditional imputation

An approach that makes more plausible assumptions is to use the relationships observed in those settings with complete data to predict unit costs in those centres where this information is unavailable. In this example, the relationship of study specific unit costs with reference costs and covariates could be estimated using an ordinary least squares (OLS) regression model as:

$$UC_{1k} = b_0 + b_1 UC_{2k} + b_2 x_{1k} + b_3 x_{2k} + b_4 x_{3k} + e_k \qquad (1)$$

Information on centre-level covariates could then be used to predict unit costs in those centres where study-specific unit costs are not measured:

$$\hat{UC}_{1k} = \hat{b}_0 + \hat{b}_1 UC_{2k} + \hat{b}_2 x_{1k} + \hat{b}_3 x_{2k} + \hat{b}_4 x_{3k} \qquad (2)$$

This approach no longer assumes that the data are MCAR, instead the unit costs are assumed to be missing conditional on reference costs and centre-level covariates. This weaker assumption, known as 'missing at random' (MAR) may be more plausible. An important limitation of this method is that for each centre with missing data it uses a single predicted value. As well as understating the variance, this distorts the correlations in the data, for example between

individual resource use and unit cost. Clearly, an additional practical problem is that this approach requires complete information on all the covariates, which in this example is only available in 18 centres.

Multiple imputation (MI)

MI is based on the principle of conditional imputation, and again assumes that the data are MAR (Rubin 1987). However, the key advantage of MI compared to conditional imputation is that it recognises the uncertainty in the imputation process. The imputed values are not single predictions, rather they are drawn from the predictive distribution of the missing data given the observed data. Under MI each missing value is replaced by a set of m>1 simulated values. The result is that there may be variation across the m imputed datasets, which reflects the uncertainty in the imputation process. Each imputed dataset should then be analysed using exactly the same method, so in a multicentre CEA the same multilevel model may be run m times, and the results stored. The stored results should then be combined across the different datasets to calculate a measure of the total variance that reflects the within and between imputation uncertainty. An appropriate way of calculating the total variance is using 'Rubin's rules' (Rubin 1987).

So if the CEA is aiming to estimate g, for example the mean incremental cost in the population of interest, then for each of the m datasets the incremental costs can be estimated as $\hat{g}_l$ (where l = 1…m) and then the overall estimate is simply the average across the m imputations $\bar{g} = \sum_{l=1}^{m} \hat{g}_l \Big/ m$.

The overall uncertainty surrounding the estimate $\bar{g}$ combines the within and between imputation variance. The within imputation variance is again taken as an average:

$$\bar{u} = \sum_{l=1}^{l} u_l \Big/ m \qquad (3)$$

The between imputation variance is:

$$B = \frac{1}{m-1} \sum_{l=1}^{m} (\hat{g}_l - \bar{g})^2 \qquad (4)$$

To give the total variance: $T = \bar{u} + (1 + 1/m)B$ (5)

The square root of T is the overall standard error of $\bar{g}$.

Section 3: Applying MI

A key issue when developing an imputation model is which variables to include. The imputation model is not required to subscribe to theory, either in terms of the variables for inclusion or with regard to functional form. Nor does it have to provide a parsimonious description of the data. As Schafer and Graham (2002) state:

"The (imputation) model is merely a device to preserve important features of the joint distribution (means, variances and correlations) in the imputed values."

Although the imputation model should not be theory driven, all variables required in a subsequent analytical model and all variables associated with missingness should be included. In this case study, a higher proportion of centres in the sample missing unit costs were teaching hospitals (30 %) compared to those with observed unit costs (12%). It was therefore important to include this variable in the imputation model.

The relationship between covariates and reference costs was examined using data from 95 Trusts in the ICNARC (2002-2003) and reference cost databases (2002-2003) (including 18 centres in the PAC-Man CEA). OLS regression models were fitted, and showed that average casemix, volume of patients, and teaching hospital status explained a reasonable proportion of the variation in unit costs across trusts (adjusted R^2>=0.20). Furthermore, the correlation between the two measures of unit costs (specific unit costs and reference costs) was fairly high (0.54) in the 23 centres where both measures were available. To address the issue that multivariate missingness limited the number of centres in the analytical sample, we conducted MI using MICE (Multiple Imputation with Chained Equations) which has been widely used in the general medical statistics literature to tackle problems of multivariate missingness (Royston 2005).

Section 4: Multilevel models (MLMs) for incremental cost and cost-effectiveness analysis

After applying MI to estimate unit costs, total costs per patient can be calculated for each imputation dataset. It is then appropriate to analyse each imputed dataset using the same MLM. In the notation below subscript i denotes the individual (i=1…1014), j the treatment group (j= 0 or 1) and k the centre (k= 1…60). As the cost data in this study are highly skewed we fit a MLM with a gamma distribution (equation 6) (Nixon and Thompson 2005), where q_{ijk} is the mean and r_j the shape of the gamma distribution:

$$
\begin{aligned}
&C_{ijk} \sim \text{Gamma}(q_{ijk}, r_j), \\
&q_{ijk} = m_k + g_k t_{ijk} \qquad \text{subscript } j = 0/1 \text{ according to treatment group} \\
&g_k \sim \text{Normal}(g, t^2) \qquad (6)
\end{aligned}
$$

The mean incremental cost g is allowed to differ across the centres by including random effects that follow a normal distribution with mean g and variance t^2. The mean cost in the control group, m_k, also differs across the centres by specifying a different, fixed effect in each centre.

This framework can be extended to estimate incremental cost-effectiveness by assuming that costs and effects are drawn from a bivariate distribution while still allowing for heterogeneity across treatment centres. Costs (C_{ijk}) are again assumed to have a gamma distribution and effects (E_{ijk}) a normal distribution, with the centre-specific mean incremental costs and effects given by g_{Ck} and g_{Ek}. Each of these random effects is assumed to follow a normal distribution with overall means g_C and g_E respectively. The variances in these random effects, or heterogeneity across the centres, are given by t_C^2 and t_E^2. The potential correlation between the individual costs and effects is recognised through the parameter b_j, in that the predicted incremental effect θ_{Eijk} partly depends on the cost C_{ijk} through the parameter b_j. The correlation between the centre-specific mean incremental costs and effects is recognised through the parameter j.

$$
\begin{aligned}
&C_{ijk} \sim \text{Gamma}(q_{Cijk}, r_{Cj}) && E_{ijk} \sim \text{Normal}(q_{Eijk}, s_{Ej}^2) \\
&q_{Cijk} = m_{Ck} + g_{Ck} t_{ijk} && q_{Eijk} = m_{Ek} + g_{Ek} t_{ijk} + b_j (C_{ijk} - q_{Cijk}) \\
&g_{Ck} \sim \text{Normal}(g_C, t_C^2) && g_{Ek} \sim \text{Normal}(g_E, t_E^2), \\
& && \text{corr}(g_{Ck}, g_{Ek}) = j \qquad (7)
\end{aligned}
$$

Estimation

The analysis compared an approach that estimated study-specific unit costs (costs per day in ICU) in each centre using MI (MI unit costs), with the original analysis that used average unit costs from the reference cost database (average reference costs). To estimate incremental costs and incremental effects we fitted MLMs with gamma (costs) and normal (effects) distributions. To estimate incremental cost-effectiveness we applied the bivariate MLM described (equation 7). The overall estimates from this MLM were used to report mean incremental net benefits (INB)

and cost-effectiveness acceptability curves (CEACs). The shrunken estimates from this MLM were used to report centre-specific incremental costs and incremental cost-effectiveness. The MI unit costs were estimated in STATA using the ice command (Royston 2005), and the MLMs fitted in WinBUGS using Markov Chain Monte Carlo (MCMC) methods (Gilks et al. 1996). For the MI unit costs each resultant estimate of incremental cost or cost-effectiveness was averaged across the five imputed datasets and the total variance was calculated by applying Rubin's rules.

Results

This section compares results with MI unit costs and those using average unit costs from NHS reference costs. Centre specific estimates are presented for those five centres (A to E) in the group without observed study-specific unit with the most patients in the RCT.

Table 1 shows that the mean MI unit cost across all 60 centres (£1,201 per ICU bedday) was similar to the mean from NHS reference costs (£1,292). However, whereas the conventional approach uses a single estimate, the mean MI unit cost had an accompanying SE (37.7). Table 1 illustrates how MI recognises the uncertainty both within and between imputations. For example, for imputation 1 the imputed unit cost varied across centres A-E from £1,162 to £1,445. The variation across imputations can be illustrated by centre A where the unit cost varied from £1,001 (imputation 4) to £1,445 (imputation 1). The total variance (1428; SE=37.7) across all 60 centres reflects the variance across (626) as well as within (mean= 647) imputations. For the 30 centres with observed cost data the total variance was relatively low as the only variance was 'within imputation', the same value was used for each centre across imputations.

The overall effect on incremental costs of using MI unit costs rather than average unit costs was fairly small (Table 2). The mean incremental cost was £724 (MI) compared to £599 (average unit costs). In the 30 centres missing unit costs, the incremental LOS was negative. As the MI unit cost was generally lower in these centres compared to the average unit cost, under MI a lower value was assigned to the reduction in LOS in these centres. The net overall effect was that MI was associated with increased incremental costs. At a centre-level, the effect of using MI unit costs versus average unit costs varied according to the difference in the unit cost and the incremental LOS in the particular centre (Table 2). The variance in the overall incremental cost

was smaller following MI compared to using average unit costs. The reason for this is that using average unit costs ignored the negative correlation between resource use and unit costs, the MI recognised this correlation which led to lower variance in incremental costs across the centres.

The results from comparing incremental costs with MI unit costs versus average unit costs are shown for selected centres A to E in Figure 1. For both unit costing approaches there were wide variations in the *observed* mean incremental costs across centres. However, these observed incremental costs were very imprecise, costs were highly skewed and clustered within centres. These issues were tackled by using the gamma MLM to estimate incremental costs. The shrunken centre-specific estimates from the gamma model were closer to the overall mean, and more precisely estimated even when based on average unit costs. When the MI unit costs were used, there was even less heterogeneity across the centres, the centre-specific shrunken estimates were closer to the overall mean and there were further gains in precision. While the overall mean incremental costs were similar across approaches, the most precise estimates were for the gamma MLM that used MI unit costs.

Table 3 summarises the incremental cost and cost-effectiveness results with average unit costs versus MI unit costs. The results from the univariate MLM show that heterogeneity in the incremental costs (t^2) was smaller (4,278 versus 10,370) and more precisely estimated (2,128 versus 16,270) following MI compared to average unit costs. The results for the MLM estimating incremental QALYs highlight that there was considerable heterogeneity in incremental effects across the centres (t^2=20.29; SE=0.94). However, these univariate analyses ignore the high correlation between costs and effects (correlation coefficient = 0.30 for No PAC; 0.28 for PAC groups). The bivariate MLM allowed for this correlation, and reported less heterogeneity across centres in either costs or QALYs than the corresponding univariate models.

The bivariate model found that the overall effect on incremental costs of using MI unit costs versus average unit costs was relatively small (872 vs 845). However, as the bivariate model recognises the correlation between costs and QALYs, using MI versus average unit costs has an impact on the estimate of incremental QALYs (0.13 vs 0.11) and the INB (1,728 vs 1,409 at l =£20,000 per QALY). The results from this model show that using MI versus average unit

costs increases the heterogeneity across centres in the estimate of incremental costs (t^2=489 vs 21.8). As for the univariate model, this centre-level variance is more precisely estimated following MI rather than average unit costs.

The CEACs reporting cost-effectiveness across all centres further illustrate that using MI versus average unit costs, has a small positive impact on the QALY gained from the intervention (Figure 2). Hence the probability that No PAC is cost-effective is slightly higher once l exceeds £5,000 per QALY. The CEACs for selected centres (A-E) are calculated using the shrunken estimates from the bivariate model. The results illustrate that there is greater heterogeneity in cost-effectiveness across the centres if MI unit costs rather than average unit costs are used. Although in 4 out of 5 centres the main cost-effectiveness results are unchanged, for centre B the probability that the intervention is cost-effective is lower at all levels of the ceiling ratio following MI rather than average unit costs, for example when the threshold is £20,000 per QALY, the probability the intervention is cost-effective falls from 0.50 to 0.30.

Discussion

Important recent advances have been made in the way CEAs have incorporated statistical uncertainty (Willan and Briggs 2006). However, one aspect of uncertainty that has received little attention in the CEA literature is the uncertainty surrounding unit costs; here a common approach is to apply average unit costs across health care settings. This runs counter to the cost function literature which suggests unit costs can vary widely across health care settings because of for example differences in technical efficiency, size of health care unit or relative factor prices (Raikou et al. 2000). This paper extends the literature on methods for CEA by presenting an approach, multiple imputation, that recognises unit cost variation across centres, and imputes unit costs for each centre. The net result is that estimating unit costs with MI, preserves correlations in the data, leading to less biased more precise estimates of cost-effectiveness than using average unit costs. In the case study presented the approach based on average unit costs from NHS Reference costs understated the overall INB of the intervention, but in certain centres using average unit costs overestimated the cost-effectiveness of the intervention.

While economic theory may encourage collecting or accessing unit costs in each centre (Heathfield and Vibe 1981), this may prove impractical and has high research costs. MI makes an

efficient use of research resources by imputing unit costs in all centres using unit costs collected in a subsample of centres, while recognising the statistical uncertainty inherent in this process. The comparator presented here was average unit costs from NHS reference costs. The comparison could be extended to include other approaches taken in the literature, for example selecting centres according to different criteria e.g. convenience, geographical spread, type of hospital, most patients in RCT, or taking a random sample of unit costs from one centre.

From the viewpoint of a national decision maker, the most important metric may be the overall cost-effectiveness of the intervention at a national level, results at a local level may be of limited interest. However, even in this context, the choice of unit costing method can matter; using MI to impute centre-specific costs may lead to differences in the overall INB compared to using average unit costs. These differences may occur if, the unit costs are not MCAR, if the incremental resource use differs by centre, or if there are important correlations in the data (e.g. between unit costs, incremental resource use and outcomes). Using local information on cost-effectiveness may run contrary to the objective of national agencies such as NICE who aim to recommend interventions that can improve the geographical equity of care provision. However, introducing a technology generally based on national averages may reduce the efficiency of care provision in some centres. A method that estimates centre-specific unit costs and shrunken estimates of incremental cost-effectiveness appropriately recognises centre-level variations. In this study the results of an appropriate model for estimating cost-effectiveness (the bivariate model, with gamma distribution for costs) found that using average unit costs underestimated heterogeneity. For some centres using average unit costs overstated the cost-effectiveness of the intervention. A further question this raises is why such local variation exist, is it attributable to exogenous factors such as teaching hospital status, or size of unit? These variables are all included in the imputation model, so it will be possible to extend the MLM to present cost-effectiveness results stratified by characteristics relevant to policy-making.

A further extension would be to compare other approaches to imputing unit costs apart from MI. For example, previous studies have used maximum likelihood methods for dealing with missing data. This approach also relies on assuming that the data are MAR. A key problem with applying this method to unit cost estimation is that it would require including in a 'single stage' all the

variables that may explain missingness. Unlike MI, a separate model is not used for 'imputation' and 'analysis' and so covariates are included in the model that economic theory may suggest should not be included in the analytical model for estimating unit costs. Another approach would be to extend the modelling to be more 'fully Bayesian'. While the approach described is partly Bayesian, for example through the use of external data for imputation, and estimating cost-effectiveness by MCMC, this could be extended by using MCMC to 'impute and analyse' in one stage (Cooper 2005).

Although previous studies have applied MI to missing data in CEA, there are some important differences in the context of imputing unit costs. In particular, it is necessary to use information beyond that routinely collected in a CEA. In this example, it was possible to access data from the ICNARC dataset and develop the imputation models on a larger range of centres (n=95) than in the CEA (n=60). The dataset on covariates and centre characteristics predicted unit costs well and it was reasonable to assume that unit costs were MAR, but this assumption that underlies MI does warrant further consideration across a range of different applications.

In conclusion, this study demonstrated the use of a statistical approach, MI, that can fully recognise statistical uncertainty when estimating centre-specific unit costs. This approach is consistent with economic theory, makes fuller use of available information and can lead to more precise, less biased estimates of cost-effectiveness than using average unit costs. The case study demonstrated that MI can lead to somewhat different cost-effectiveness results, in particular at a centre-level. MI is of general use for imputing missing unit costs, as well as missing resource use and outcome data in CEA.

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Table 1: Imputed Unit costs (£ per ICU bedday] for all 60 centres, and for five selected centres (A to E).

	Imputation 1	Imputation 2	Imputation 3	Imputation 4	Imputation 5	mean imputations 1-5
mean (SE); all 60 centres	1209(26.6)	1222(25.9)	1216(28.2)	1198(23.7)	1159(25.5)	1201(37.7)
mean (SE); 30 centres missing unit costs	1182(38.5)	1208(36.7)	1195(43.0)	1160(28.7)	1082(29.4)	1166(65.2)
mean (SE); 30 centres observed unit costs	1239(36.9)	1239(36.9)	1239(36.9)	1239(36.9)	1239(36.9)	1239(36.9)
Selected centres						
A	1445	1340	1250	1001	1337	1275
B	1337	884	1712	1337	1063	1266
C	1326	1259	1167	1382	1208	1268
D	1337	1208	1337	1063	1162	1221
E	1162	971	904	1208	884	1026

Table 2: Mean (SE) Incremental LOS in ICU [days] and mean (SE) incremental costs based on mean unit cost from Reference costs [£1,292] versus unit cost from multiple imputation (MI). Results presented across all centres and for selected centres A-E.

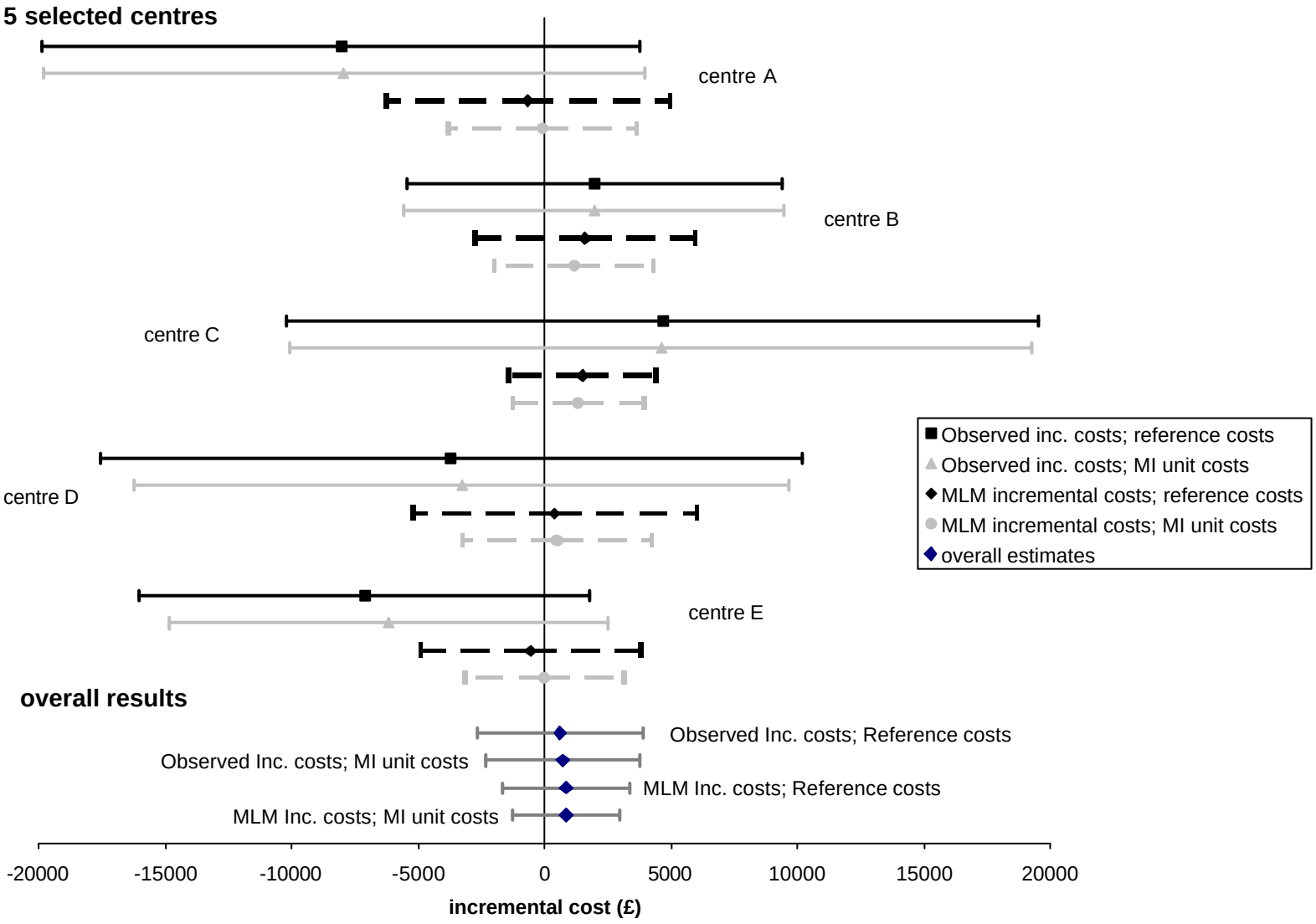
Centre	N	Mean (SE) Incr. LOS	Mean MI unit cost	Mean (SE) Incremental cost Reference cost Unit cost	Mean (SE) Incremental cost MI Unit cost
Overall mean across all 60 centres	1014	-0.09(1.14)	1201(37.7)	599(1,668)	724(1,549)
mean 30 centres missing unit costs	366	-2.71(1.80)	1166(65.2)	-2,873(2,683)	-2,128(2,374)
mean in 30 centres observed unit costs	648	1.40(1.46)	1237(36.9)	2,565(2,123)	2,332(2,018)
Selected centres					
A	61	-5.56(4.10)	1275	-8,042(6,026)	-7,939(6,071)
B	45	1.44(2.77)	1266	1,984(3,794)	1,946(3,834)
C	35	2.83(5.21)	1268	4,680(7,592)	4,610(7,482)
D	28	-4.07(2.40)	1221	-7,107(4,549)	-6,815(4,430)
E	33	-4.39(5.71)	1026	-5,985(9,972)	-4,812(8,611)

Table 3: Summary of results from univariate MLM s that separately estimating incremental costs (£) and incremental effects. Results from a bivariate MLM estimating incremental cost-effectiveness. All results are presented using the average unit cost from Reference costs versus MI unit costs.

	Reference costs unit cost	MI Unit costs
Univariate costs*		
Mean (SE) incremental costs	851(1,273)	883(1,075)
t^2 (SE)	10,370(16,270)	4,278(2,128)
Univariate effects		
Mean (SE) incremental QALYs	0.12(0.29)	0.12(0.29)
t^2 (SE)	20.29(0.94)	20.29(0.94)
Bivariate costs and effects #		
Mean (SE) incremental QALYs	0.11(0.30)	0.13(0.29)
t^2 (SE)	0.23(0.24)	0.32(0.28)
Mean (SE) incremental costs	845(1,310)	872(1,317)
t^2 (SE)	21.8(17.2)	489(277)
Mean (SE) INB(l =£20,000 per QALY)	1,409(5,413)	1,728(4,798)

* Note that the Univariate MLMs assumes a gamma distribution for costs, # the bivariate MLM assumes that costs have a gamma distribution and effects follow a normal distribution.

Figure 1: Incremental costs from observed data and shrunken estimates from univariate MLMs. Incremental costs presented for mean unit costs from Reference costs versus MI unit costs. Results are overall (60 centres) and for selected centres A to E.



* Note that the Univariate MLMs assumes a gamma distribution for costs

Figure 2: CEACs comparing the probability that the intervention is cost-effective using MI unit costs versus mean reference costs. CEACs are calculated using the overall results from the bivariate MLM.

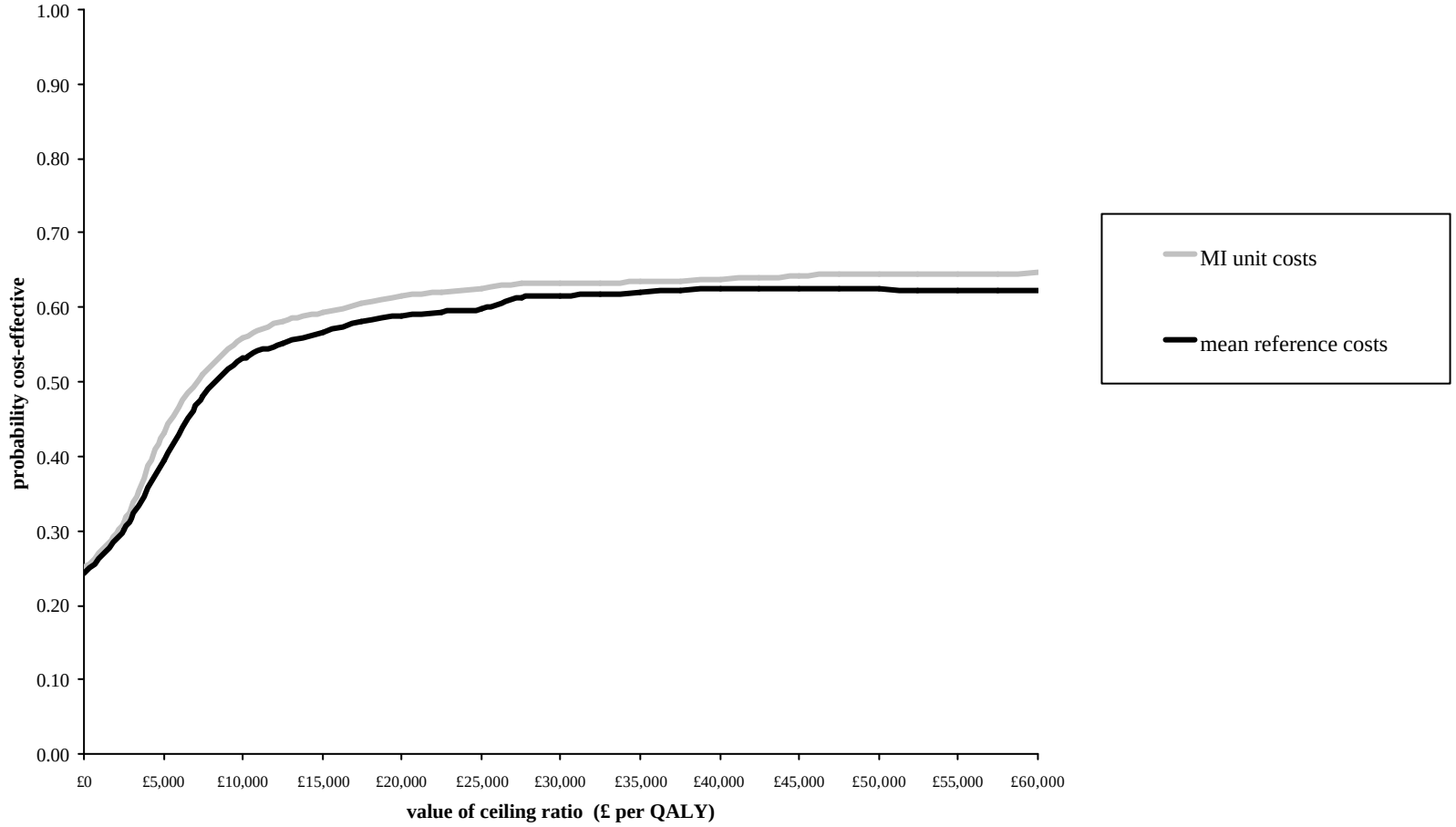
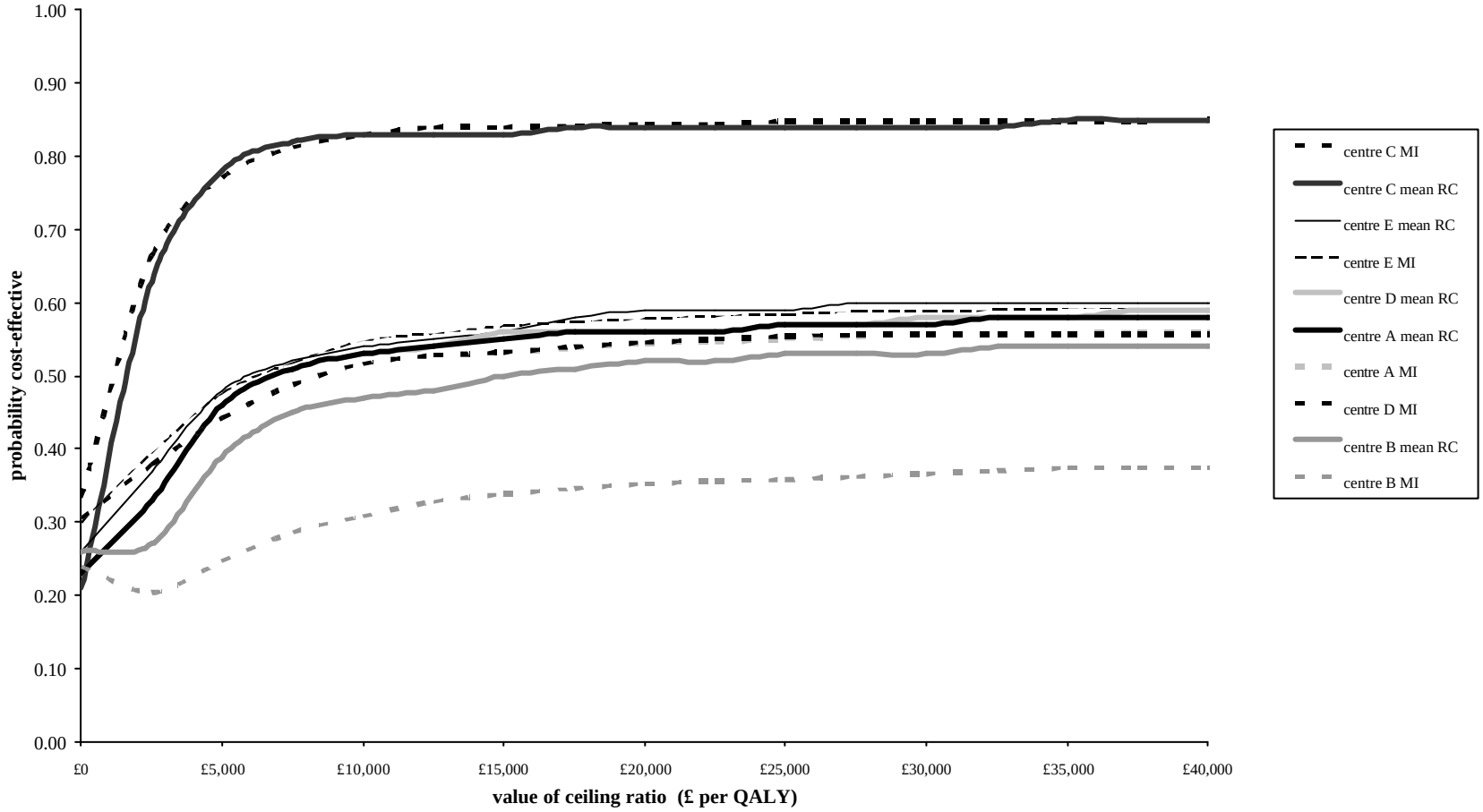


Figure 3: CEACs comparing the probability that the intervention is cost-effective using MI unit costs versus mean reference costs. CEACs calculated using the centre-specific shrunken estimates from the bivariate MLM, for centres A to E.



Note that the CEACs for centre A with MI unit cost and centre D with mean RC are only partially visible as they are almost identical to the CEAC for centre D MI and centre A mean RC respectively