Conducting economic evaluations of low volume technologies: a case study of small bowel transplantation in paediatric patients

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Introduction

Low volume treatments, such as transplantation and ventricular assist devices, are suitable for treating small numbers of patients and are often expensive. Data on the cost-effectiveness of treatments is desirable in order to inform resource-allocation decisions. However, reliable evidence on the cost-effectiveness of low volume technologies is often difficult to obtain because of the small numbers of patients from which to obtain data. Following an approach by NSCAG to conduct an economic evaluation of the programme of small bowel transplantation in paediatric patients, this paper aims to present and compare four possible approaches to the analysis of the cost effectiveness of this particular low volume technology that NSCAG funds.

Intestinal failure is caused by the inability of the intestine to maintain nutrition or intestinal fluid [1]. Patients with intestinal failure are often treated with parenteral nutrition (PN), which involves the administration of nutrition solutions through a long-term central venous catheter [2]. The treatment may be supplied in the home environment, home PN (HPN), which avoids frequent and lengthy hospitalisations. HPN is a complex and costly treatment, and despite dramatic improvements, long term management with PN can cause life-threatening complications such as liver failure and pulmonary embolism [3,4]. Small bowel transplantation (SBTx) is considered as an alternative to HPN for some patients.

The introduction of new immunosuppresant drugs, particularly tacrolimus, in the 1980s has greatly improved the survival prospects of patients undergoing SBTx [5]. In Britain it is estimated that two patients per million population require a small bowel transplant each year, and that half of these patients will be paediatric cases [6]. To date, no randomised controlled trial (RCT) has been conducted for small bowel transplantation (SBTx), and although there is some evidence regarding short-term survival in paediatrics [5,7], there is no evidence regarding the cost-effectiveness of the intervention in paediatric or adult patients. Thus, in conducting an economic evaluation of SBTx, we were faced with two problems: a small sample size from which to obtain data and the absence of a control group as found in conventional RCTs.

Although seen as the gold standard for economic evaluations, RCTs are often inappropriate for the economic evaluation of low volume technologies. The small

sample size available for the evaluation may result in the trial lacking power to detect clinically significant differences. RCTs are also problematic for the evaluation of transplantation technologies. Blinding is impossible. An unblinded trial might be ethical in terms of clinical equipoise, but would probably have to involve matched pairs of patients, both suitable for the same organ, randomised when an organ becomes available. This process might well be deemed unacceptable.

Britton et al [8] have argued that randomisation is unnecessary, inappropriate, misleading and impossible. To overcome the problems of small numbers they suggest the need for more observational studies (non-randomised studies). The best type of observational study to use is case-control studies because they are suited to the evaluation of rare diseases (small numbers) and are not as expensive as RCTs. However, this also comes with its fair share of problems, namely, selection bias. In our study, there is an element of selection bias as, once on the waiting list, patients are selected for a transplant on the basis of clinical need, rather than a first-come, first-served basis. It may be possible to conduct a case-control study for small bowel transplantation, if a control group could be observed from a centre treating similar patients, but where there is a reluctance to refer patients for a transplant as the benefit has not be proven.

Other methods proposed to overcome the problems of small sample size is to change the level of certainty [9]. A Bayesian approach can be used to analyse the results, because it will give probabilities that the clinical effect lies in a particular range (and also the size is the most likely effect). This approach provides probabilities that can be used in formal decision analysis, or extrapolated to clinical practice. These probabilities are calculated on the basis of the observed data and a prior distribution of probabilities. However, owing to the time constraints of the project, this approach was not explored.

Despite the problems of small sample size and the lack of a control group, other researchers have conducted economic evaluations in similar situations. An economic evaluation of heart transplantation [10] overcame problems associated with small sample sizes and the lack of a formal control group. The experience of transplanted patients was compared to a control group, using patients' waiting list experiences to estimate the without-transplantation experience.

Prognostic models have been used in economic evaluations of liver transplantation [11,12] to estimate the without-transplant experience in the absence of a control group. These models enable patients to be used as their own controls and increase sample size.

This paper presents a comparison of four possible methods to estimate the relative cost-effectiveness of small bowel transplantation in paediatric patients. The analysis utilises an 'intent to transplant' approach by comparing transplanted patients with four alternative control groups which might be used in the absence of a formal control group. These comparator groups include a combination of data from prognostic models and the waiting list experience of patients.

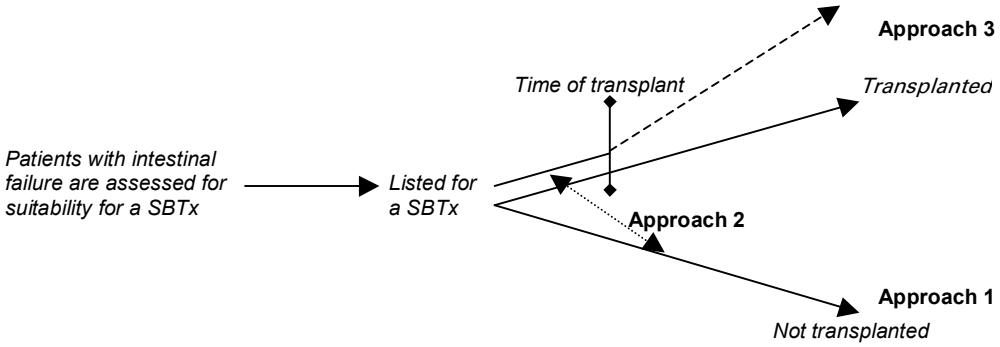
Methods

Patient sample

We recruited paediatric patients with intestinal failure who were listed for a small bowel transplant at Birmingham Children's Hospital (BCH) between 1st April 1997 and 1st April 2001 into the study. Patients were followed for thirty months (2.5 years) from their first assessment for a transplant or until their date of death.

Approaches taken to the analysis

The four approaches taken to the analysis are detailed below and illustrated by Figure 1. In each approach patients transplanted during the study period are compared to a control group. The data included in the control group varies in each approach to the analysis.



Approach 4 = Approach 1 + Approach 3

Figure 1: An illustration of the four approaches

Approach 1: Comparison of transplanted patients with the waiting list experience of patients who were not transplanted during the study.

Patients who were listed and transplanted (L-Tx) were compared to patients who were placed on the waiting list but not transplanted (L-NTx) during the study period. The L-NTx group consists of patients who died whilst on the waiting list, were removed from the waiting list, or were still awaiting a transplant at the end of the study period.

Approach 2: Comparison of transplanted patients with the waiting list experience of all patients

The second comparison compares the experience of transplanted patients with the waiting list experience of *all* patients. Thus the control group consists of the waiting list experience of patients who were not transplanted during the study (L-NTx) and the waiting list experience of the transplanted group (L-Tx).

Approach 3: Comparison of transplanted patients with their waiting list experience and the use of prognostic models

The experience of transplanted patients (L-Tx) was compared to an estimate reflecting their without-transplantation experience. As well as data relating to each patient's waiting list experience, a 'shadow' was estimated for each transplanted patient, to reflect his or her likely experience in the absence of transplantation. A prognostic model was designed to predict the without transplant survival of patients using patient specific clinical data. Data relating to waiting list experience of transplanted patients were used to estimate shadow costs. Thus, each transplanted patient has observed data relating to their pre-transplant experience, plus shadow data representing their likely experience in the absence of transplantation.

Approach 4: A combination of approaches 1 and 3

The fourth comparison compares transplanted patients (L-Tx) with a control group estimated by combining Approaches 1 and 3. This control group consists of the waiting list experience of L-NTx patients (Approach 1), plus the waiting list experience of transplanted patients and their expected experience without transplantation predicted using the prognostic model (Approach 3).

Survival

The observed survival times for all patients are measured from the date of first assessment at BCH during the study period. 38.8% of listed patients alive at the end of the study did not have complete 30-month follow-up data. These patients are said to be "censored cases" and are censored at the end of the study period (1st April 2001). If censoring is ignored and the analysis performed as if data were complete, the results of the analysis would be an underestimate of the true result.

Due to the high proportion of censored observations, a censored cost technique proposed by Lin et al [13] is used to analyse the cost data. A well established statistical technique, the Kaplan-Meier method, was used to adjust for censoring in outcome data [14]. Kaplan-Meier survival analysis is used to assess differences between groups (Log-rank test). The area under the curve method is used to calculate the mean 30-month survival for each group [15].

The estimated "shadow" survival used in Approaches 3 and 4, was calculated using a prognostic model based upon patient-specific data on patient characteristics (age, gender, and type of intestinal disease) and disease severity (bilirubin levels, prothrombin time (PT), and Scheuer scores[1] [16]). The model was fitted to all patients assessed for a small bowel transplant, including those seen at BCH during the study period who were not placed on the transplant waiting list. An illustration of the sample used to derive the prognostic model is shown in Figure 2. The sample size for the prognostic model was 50, where the transplanted patients were censored at time of transplantation. The prognostic model was fitted using Cox proportional hazards modeling, where factors found to be significant predictors of survival were included in the model, these factors were bilirubin levels and PT. This model was applied to data from the transplanted patients to predict the without-transplantation survival of these patients from time of transplant.

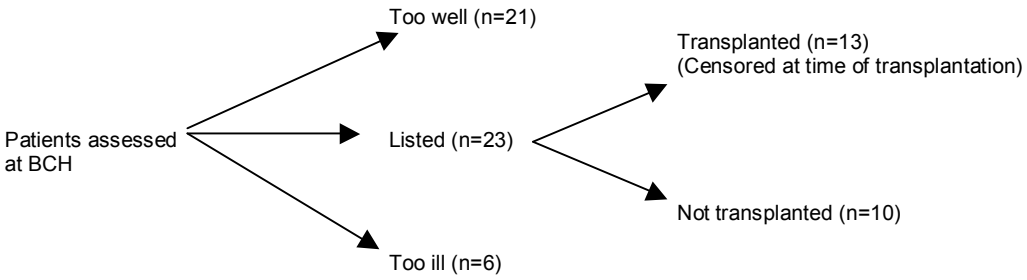


Figure 2: An illustration of the prognostic model

The predicted shadow survival from time of transplant was added to the observed waiting list data (from assessment to time of transplant) to obtain the predicted survival of the control group used in Approach 3. Patients were expected to die in the absence of

[1] Scheuer scores a clinical measure of disease severity [16]

transplantation if their expected survival, including the time on the waiting list, was less than 30 months, otherwise, they were expected to survive to the end of the study period.

Resource-use and unit cost data

Detailed information on resource use incurred at BCH was collected prospectively for each patient. Estimates of unit costs were provided by BCH for all items of resource-use and based on 1998/99 prices, with the exception of HPN and drug costs. Drug costs were obtained from the British National Formulary [17] and an average cost (per patient per day) for HPN was obtained from a commercial supplier used by BCH.

Shadow costs were estimated from the experience of transplanted patients whilst on the transplant waiting list. Each transplanted patient's own average pre-transplant daily cost was calculated, and it was assumed that patients would incur costs at this rate in the absence of transplantation. Each patient's daily cost was applied to the number of days they were expected to survive as predicted by the prognostic model. Adjustments for costs prior to death were made for patients who were expected to die within the study period in the absence of transplantation. This adjustment was made using transplanted patients' observed costs prior to death. For patients who did not die during the study, but were predicted to die in the absence of transplantation, the average cost of those patients who died was used.

Statistical analysis

The statistical computer packages S-PLUS and STATA were used for all analyses [18,19]. All statistical tests are two-sided, unless otherwise stated. A p-value of ≤ 0.05 was taken as the level for statistical significance. Bias adjusted non-parametric bootstrapping was performed in order to generate confidence intervals around the mean ratios.

Clinical information which was used to measure disease severity (13% missing), nutritional information (52% missing) and physiotherapy sessions (30% missing) was only recorded for a number of patients. In each of these cases the missing data was estimated using multiple imputation techniques. This is a Monte Carlo simulation technique where each missing data case is replaced by a set of plausible estimates, where the number of estimates required is determined by the available resource-use

data and patient characteristics to predict missing values [20]. NORM, a computer program for estimating missing data from multiple imputation techniques, was used to estimate the values for missing data [21].

Results

Patient sample

Thirteen patients were transplanted (L-Tx) during the study and 10 patients were placed on the waiting list but not transplanted (L-NTx) during the study period. Table 1 details the number of observations in the treatment (transplant) group, and in each of the four comparator groups.

Table 1: Number of observations used for each approach to the analysis

	Transplant group (all approaches)	Comparator group: Approach 1	Comparator group: Approach 2	Comparator group: Approach 3	Comparator group: Approach 4
Number of observations	13	10	23	13	23

Table 2 presents summary demographic and clinical characteristics for the sample. No statistical significant differences in the data were found between the groups. The majority of transplanted patients were placed on the waiting list for a combined liver and small bowel transplant. Two patients were listed for multivisceral transplants.

Table 2: Demographic data for the sample

	Transplant group (all approaches)	Comparator group: Approach 1	Comparator group: Approach 2	Comparator group: Approach 3	Comparator group: Approach 4
Males	8 (61.5%)	6 (60.0%)	14 (60.9%)	8 (61.5%)	14 (60.9%)
Age (months)					
Median	10	9	9	10	9
IQR	5 to 14	6 to 44	5 to 15	5 to 14	5 to 15
Type of intestinal disease					
Short gut	8 (61.5%)	7 (70.0%)	15 (65.2%)	8 (61.5%)	15 (65.2%)
Mucosal lesions	1 (7.7%)	1 (10.0%)	2 (8.7%)	1 (7.7%)	2 (8.7%)
Pseudo obstruction	4 (30.8%)	2 (20.0%)	6 (26.1%)	4 (30.8%)	6 (26.1%)
Bilirubin (μmol/L) – at assessment					
Median	168	183	168	168	168
IQR	148 to 156	6 to 439	69 to 266	148 to 156	69 to 266
Prothrombin time (seconds) – at assessment					
Median	15	15	15	15	15
IQR	13 to 18	13 to 19	13 to 18	13 to 18	13 to 18
Scheuer score 3 or 4	10 (76.9%)	6 (60.0%)	16 (69.6%)	10 (76.9%)	16 (69.6%)

Survival

Seven of the 13 transplanted patients (53.8%) survived to the end of the study period, Kaplan-Meier survival curve for this group of patients, and patients included in approaches 1 to 4 are shown in Figures 3a to 3d. It can be seen from these survival curves that the approaches give differing survival results, where approach 2 predicts significantly greater survival for the comparator than the other three approaches (χ_3^2 =12.00, p =0.007). Figure 3b shows that the survival rate is high for patients who were L-NTx and the waiting list experience of transplanted patients. In this comparator group (Approach 2), only three of the patients died during the study period, whereas with the comparator group which used prognostic models (Approach 4), 9 patients would have died during the study period.

Figure 3a - Approach 1

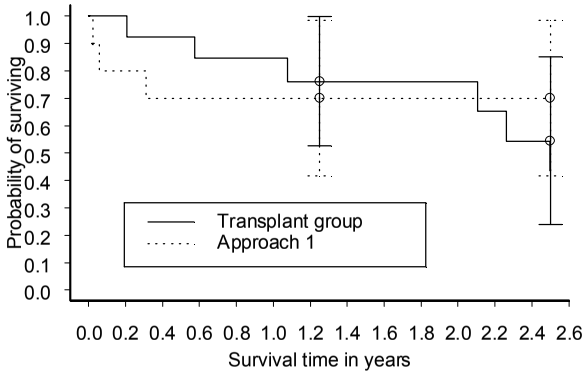
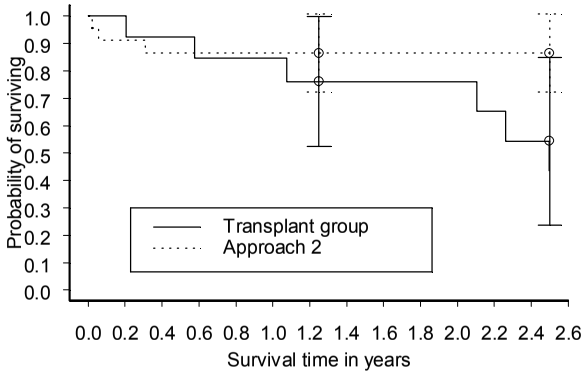


Figure 3b – Approach 2



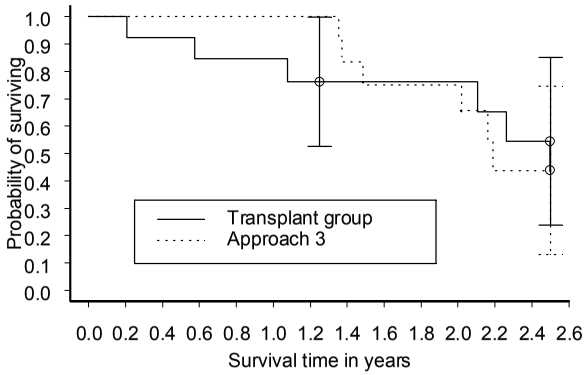


Figure 3c –Approach 3

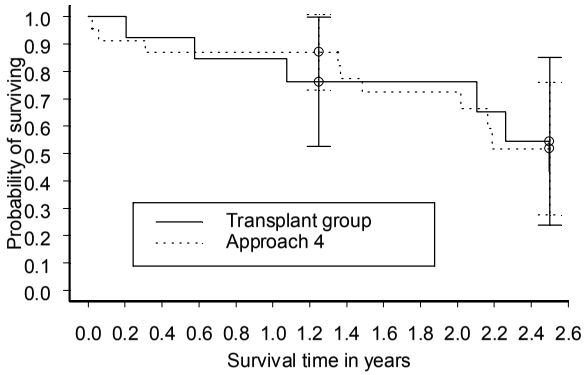


Figure 3d – Approach 4

Table 3: Mean survival to 30 months from point of first assessment presented in years

	Transplant group (all approaches)	Comparator group: Approach 1	Comparator group: Approach 2	Comparator group: Approach 3	Comparator group: Approach 4
Mean	1.98	1.79	2.19	2.16	2.09
95% CI	1.55 to 2.49	1.22 to 2.50	1.87 to 2.5	1.95 to 2.47	1.75 to 2.47

Table 3 shows that the average survival to 2.5 years from assessment was greater for patients who were transplanted compared with patients in comparator group 1. When using approaches 2, 3, and 4, transplantation appears to reduce survival slightly (as seen in figure 3b, 3c, and 3d respectively), although this was not statistically significant. However there were no significant differences in survival between transplanted patients and any comparator group.

Costs

Table 4 shows details of the per-patient costs for the group of transplanted patients and the comparator groups from each of the four approaches. The median costs of the comparator group are similar for approaches 3 and 4. There are no statistically significant differences between the transplanted group and the comparator group using approaches 3 or 4. However, the difference in costs between the transplanted and comparator groups are statistically significant using Approach 1 (χ_1^2 = 10.400, p = 0.001) and using Approach 2 (χ_1^2 = 7.025, p = 0.007).

Table 4: Summary costs (per patient)

	Transplant group (all approaches)	Comparator group: Approach 1	Comparator group: Approach 2	Comparator group: Approach 3	Comparator group: Approach 4
N	13	10	23	13	23
Mean (SD)	£235,858 (£110,850)	£89,845 (£61,819)	£132,224 (£123,738)	£328,538 (£230,830)	£229,047 (£214,444)
Median	£230,286	£98,508	£104,780	£211,415	£189,672
IQR	£182,517 to £277,774	£31,129 to £122,038	£43,018 to £174,930	£189,672 to £300,712	£111,779 to £262,796

Cost-effectiveness results

The bootstrapped survival results presented in Table 5 show that there appears to be a survival gain from transplantation when using Approaches 1 and 2 to estimate the experiences without transplantation, but not when using Approaches 3 and 4. The survival gain from transplantation appears greatest when compared to the waiting list survival of all patients placed on the transplant waiting list (Approach 2: survival gain = 0.814 years). Both of the approaches that suggest a survival gain from transplantation use only experience on the waiting list to estimate the situation without transplantation. The approaches using the prognostic model to estimate survival in the absence of transplantation suggest that overall survival is reduced by transplantation.

The mean incremental cost of providing small bowel transplantation is over £100,000 estimated using Approaches 1 and 2. Using the prognostic models and the waiting list experience of transplanted patients to estimate the comparator group (Approach 3), it appears that transplantation is cost-saving, a result of the reduction in survival.

The results from the bootstrapping technique were unstable for Approaches 1 and 4, due to some very small differences in survival, therefore it was not possible to estimate confidence intervals around the mean. In these two cases, the mean ICERs have been calculated by dividing the bootstrapped mean incremental costs by the bootstrapped incremental survival.

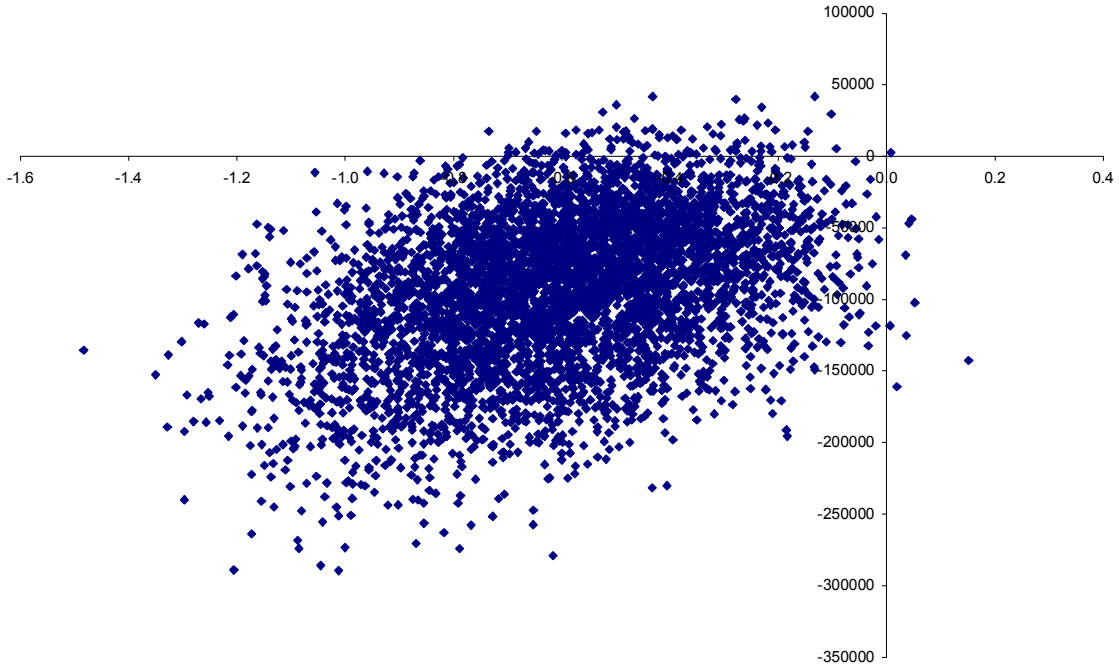
Owing to these problems resulting from the bootstrapping technique we also adopted a net benefit approach using the value of £30,000 per additional life year gained. The value of £30,000 was chosen as this has been reported as appearing to be the benchmark cost per QALY which NICE uses to inform its decisions [22]. As we can see from Table 5 the net benefit differs substantially across all approaches. Only one of the four approaches (Approach 3) indicates a net benefit from small bowel transplantation assuming the value of £30,000 per life year gained. In this approach, the positive net benefit arises because the reduced survival from transplantation is offset by a larger reduction in costs. To illustrate this, Figure 4 displays the cost-effectiveness plane from using Approach 3. The majority of mean observations fall in the bottom-left quadrant where both incremental costs and survival gain are negative. The 95 percent confidence intervals around each of the net benefit estimates are large.

Table 5: Cost-effectiveness results from each of the four approaches (mean values are presented with 95% confidence intervals in parenthesis)

	Approach 1	Approach 2	Approach 3	Approach 4
Survival gain	0.371 (-0.396 to 1.128)	0.814 (0.172 to 1.353)	-0.608 (-1.106 to –0.194)	-0.190 (-0.811 to 0.384)
Incremental costs	£145,908 (£85,570 to £225,014)	£103,483 (£27,023 to £183,982)	-£93,510 (-£233,073 to –£17,225)	£6,620 (-£110,691 to £101,201)
ICER	£393,283 (confidence intervals not available)	£246,272 (£25,010 to £318,746)	£168,345 (£19,448 to £613,270)	-£34,842 (confidence intervals not available)
Net benefit	-£134,778 (-£205,666 to -£90,671)	-£79,063 (-£152,375 to -£7,869)	£75,270 (-£7,308 to £210,358)	-£12,320 (-£97,521 to £100,345)

[Note: The bootstrapped survival results presented above were based on mean observed survival times without using the area under the curve method to adjust for censored data. This is why the gain in survival is positive in the table above, but would not be if worked out from the data presented in Table 3. We are currently reanalysing the bootstrapping with an adjustment for censoring]

Figure 4: Distribution of mean ICERs comparing transplanted patients (L-Tx) to their shadow data (Approach 3)



Discussion and conclusions

This study has attempted to overcome the problems of evaluating the cost-effectiveness of a low volume technology where a randomised controlled trial is not possible. This has included a comparison of four possible approaches to estimating a comparator group with which to compare small bowel transplantation. These approaches included using the waiting list experience of patients and prognostic models. The different approaches used in this paper were chosen as they represented the methods used by other researchers facing similar problems when conducting economic evaluations in the absence of a control group, or combinations of these methods [10, 11, 12].

However, the methods for each comparator group differ considerably and each method provides results that are substantially different. Our study indicates that approaches 1 and 2 show that there is survival gain from transplantation, however this gain varies across both. The survival rate is higher for patients who were in the comparator group (Approach 2) compared to patients who were transplanted (87% vs. 53.8%). Thus, the survival difference for the transplanted patients is higher than this comparator group

(mean gain = 0 .814). This may indicate that our comparator group in this approach is not very stable.

If we accept that the waiting list experience of patients can be used as a proxy for the likely experience of patients in the absence of transplantation, then Approach 2 can be preferred over Approach 1. The comparator group in Approach 1 is restricted to the waiting list experience of patients who were not transplanted during the study period. However, Approach 2 makes the best use of all the available waiting list data by also including the waiting list data of transplanted patients censored at the time of transplant.

The extent to which approaches 3 and 4 is preferred depends upon confidence in the prognostic model to predict the likely experience without transplantation. To a large extent this will be determined by the amount to which the experiences of patients not placed on the transplant waiting list, either because they were too ill or too well, can be explained by the factors included in the prognostic model. It will depend upon whether the experiences of patients not listed for a transplant can reflect the experiences of transplant candidates in the absence of transplantation. Of the patients included in the prognostic model cohort, it is possible that those considered too well or too ill for a transplant are at different stages of disease progression than those placed on the waiting list. Patients considered too well may be presenting at BCH early in the disease, and may undergo another assessment at a later date when their condition has worsened. Patients considered to be too ill to place on the waiting list, may be presenting at BCH later on in their disease progression, and it is also possible that they may have been suitable candidates for small bowel transplantation had they been presented at an earlier date. Ideally the results from this model should be validated using data from an alternative source, however this was not possible for the purposes of this paper.

Finally, if we accept that the waiting list experiences of patients can be used as a proxy for the without-transplant experience of patients, and have confidence in the prognostic model, then Approach 4 is the preferred approach. This uses all the available data and could be seen as a weighted average of Approaches 1 and 3.

Unfortunately we were unable to obtain a 95% confidence intervals around mean ICERs for two of the approaches. This was due to very small effect sizes for some patients, leading to very large positive and negative ICERs. A net benefit approach was also taken to the analysis to avoid the problem of being unable to obtain a distribution of mean ratios using the bootstrapping technique where the survival difference is very small.

One important point to note is that the patients in this study are not homogeneous. Further work needs to be done to see whether these results are replicated elsewhere. We hope to combine the data from BCH with that of other small-bowel transplant programmes conducted abroad. However, we have to be careful in combining data due to various biases that may arise.

One potential problem within the study is that an element of patient selection bias may exist. Within the group of patients placed on the waiting list but not transplanted during the study some are likely to have had a better prognosis than transplanted patients as transplants are offered to candidates on the basis of clinical need for a small bowel transplant and not on a 'first come, first served basis'. Thus, selection of patients due to clinical need, along with small sample size is likely to be an important confounding factor, which arises in selection bias and in turn affects the estimation of both net costs and survival for each group, respectively.

Another limitation of the study is the focus upon costs incurred by BCH. Costs are also likely to be incurred by patients were BCH is not their local hospital; also by the wider health care network including, general practitioners, community services, social services and voluntary organisations. There is also a cost in terms of the burden placed upon the family unit that is difficult to quantify, but nevertheless should be considered. These costs to the family may include the cost of travelling to BCH and the costs associated with a parent having to stop working to look after their child.

The analysis presented here focuses upon difference in life years as the primary outcome measure. Small bowel transplantation and HPN both have an impact upon the health-related quality of life (HRQL) of the patient. Other economic evaluations weight life years gained by a quality of life index to form quality-adjusted life-years (QALYs).

[23]. Unfortunately, the instruments used to generate these HRQL indices are not appropriate for very young paediatric patients, as they refer to mobility, depression and usual activities in adult terms. The Health Utilities Index (HUI2) can be used to weight QALYs, but is only suitable for patient's aged upwards of 6 years [24]. Other quality of life questionnaires are available for paediatric patients but cannot be used to weight QALYs. The Child Health Questionnaire [25] can be used in patient's aged 10 years or older. The Pediatric Quality of Life Inventory (The PedsQL) [26] has been developed in four different forms, for children and teenagers between the ages of 2-18 years. However, the median age of our study was approximately 10 months therefore these questionnaires were unsuitable for many of the patients within our study.

Another point this study has raised is to see whether there is a learning curve effect for the costs of SBTx (to see whether there is a positive relationship between volume and quantity) and also for survival of SBTx. We aim to investigate the existence of a learning curve effect from our data, but are aware that splitting the sample into even smaller groups will mean that statistically significant differences are unlikely.

We would welcome discussion on the following points:

1. The approaches used to estimate the control group.
2. Problems of the unstable bootstrapped results caused by the small differences in survival.
3. We would also like to learn of the experiences of other researchers in the evaluation of low volume technologies.
4. Using a Bayesian approach for conducting an economic evaluation of low volume technologies

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