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INFORMING THE MANAGEMENT OF PEDIATRIC HEART TRANSPLANT WAITING LISTS: COMPLEMENTARY USE OF SIMULATION AND ANALYTICAL MODELING

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ABSTRACT

A clinical intervention known as 'bridging to transplant', in which a patient is placed on life-sustaining support, can be used to increase the chance of an individual surviving until a donor heart becomes available. However, the impact of this on other patients on the waiting list and the wider implications for the resourcing of cardiac units remains unclear. Initial insights have previously been generated using a birth-death queuing model, but this model did not incorporate realistic donor-recipient assumptions regarding blood type and weight. Here we report on a complementary simulation study that examined how estimates from the analytical model might change if organ matching were better taken into account. Simulation results showed that system metrics changed substantially when recipient donor compatibility was modelled. However, the effects of blood type compatibility were countered by that of weight compatibility and when combined, these have a relatively small net effect on results.

1 INTRODUCTION

Depending on the severity of their cardiac failure, children awaiting a heart transplant in the UK are registered either as urgent or non-urgent, with priority for compatible hearts given to those with urgent status. Due to the short life expectancy of these children, the rarity of pediatric donor hearts, and the necessity for donor-recipient compatibility according to weight and blood type, there can be a lack of available donor organs or of suitable recipients when donor organs do become available (Andrews et al. 2008; Suddaby 1999). As a result, patients may die waiting for a heart and yet some donor hearts go unused (Goldman et al. 2003; McMahon et al. 2003).

To increase both the chance of an individual surviving to transplant and the use of donor organs, a clinical intervention known as 'bridging to transplant' has been introduced whereby the patients awaiting a donor heart are admitted to hospital and given life-sustaining support (Fiser et al. 2003; Gajarski et al. 2003). In the UK, such a program of bridging to heart transplant was introduced in 1998 (Goldman et al.

2003; McMahon et al. 2003). However, bridging by no means guarantees survival to transplant, is financially costly (Brown et al. 2009) and has implications for the use of scarce resources in high-intensity care units. In decisions regarding bridging strategy, the potential benefit to bridged patients would ideally be considered alongside the other implications, including the impact on transplant patients that are not bridged and the extent to which prolonged bed-occupancy affects other cardiac services. A mathematical model that relates the key variables of this complex problem and has clinical face validity could potentially be a useful tool for informing decision makers.

With this in mind, a queuing theoretic model of this system using birth-death analysis theory has been developed (Crowe et al. 2011). Illustrative results from this model have provided initial insights of interest to clinicians and managers involved in the UK pediatric heart transplant bridging program. The model was deliberately chosen to be simple and does not incorporate donor-recipient compatibility requirements related to blood type nor realistic weight-matching criteria. Adding such requirements considerably complicates the queuing theory equation and, thus far, an analytical solution has not been found. However, the impact of this simplification on the quantitative forecasts of the model, and therefore how clinically valid the model would be for use in informing decisions regarding future bridging strategy, is unclear.

In this study we used simulation to examine the importance of taking full organ matching criteria into account when assessing the overall effects of bridging and to detect whether this gives rise to gross errors. We note that although simulation has been used to address many issues surrounding liver (Howard 2001; Pritsker 1998; Ratcliffe et al. 2001; Thompson et al. 2004), renal (Abellan et al. 2006; Zenios et al. 2000) and cardiac (van den Hout et al. 2003) transplant waiting lists, to the best of our knowledge simulation or analytical methods have not been applied to the specific problem of bridging to heart transplantation in pediatric patients, other than the birth-death queuing model (Crowe et al. 2011).

2 MODELING THE PEDIATRIC HEART TRANSPLANT WAITING LIST PROGRAM IN THE UK

2.1 Birth-death queuing model

Previous work by the authors (Crowe et al. 2011) concerned modeling pediatric heart transplant waiting lists using simple queuing theory. Within this analysis, the referral of patients to a transplant waiting list was assumed to follow a Poisson process. The clinical pathways followed by patients are summarized in Figure 1. A specified proportion of these patients were assumed to be assigned, at random, to an urgent waiting list, the remaining to a non-urgent list. A given percentage of patients on the urgent list were assumed to warrant bridging on clinical grounds and, of those, a specified proportion was assumed to be assigned to bridging. The latter proportion was the mechanism used by which one could investigate a range of policy options, from zero bridging to the current UK practice of bridging all patients that meet the clinical indications.

Four classes of potential recipients were considered: non-urgent list patients and three classes of urgent cases, including those deemed to warrant bridging (partitioned according to whether or not they were assigned to it) and those judged not to warrant bridging. It was also assumed that patients do not move between classes. It was assumed that, in the absence of a transplant, patients' life expectancy following referral are negative exponentially distributed, the mean rates of death on the waiting list dependent upon the patient class.

Donor heart arrivals were assumed to follow a Poisson process. In reality, patients only receive donor hearts that are blood type and weight compatible. However, within this queuing model, two simplifying assumptions were made. Firstly, it was assumed that there are no donor-recipient matching conditions related to blood type. Secondly, recipients and patients were split into three separate weight groups (<10 kg, 10-30 kg and >30kg) and it was assumed that patients may only receive hearts from within the same weight group.

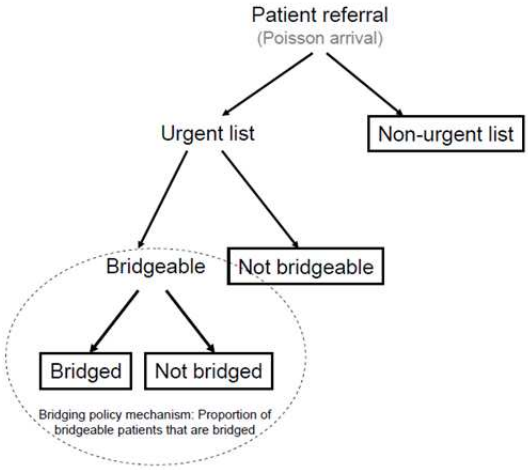

Figure 1: Flow diagram illustrating the four patient classes: non-urgent list patients, urgent list patients not warranting bridging, urgent list patients warranting bridging but not bridged and urgent list bridged patients. The proportion of patients warranting bridging that are bridged is the mechanism used to investigate possible bridging policy options.

In the allocation of donor hearts, priority was assumed to be given to patients on the urgent list and allocated at random within the urgent patient classes. In the absence of patients on the urgent waiting list, donor hearts were assumed to be assigned to patients on the non-urgent list at random.

Given this model structure, an analytical approach based on birth-death analysis was used to establish expressions for various steady state quantities such as the expected transplant rate and death rates for urgent and non-urgent patients.

Under a further assumption that all urgent patients spend their entire wait in hospital whilst non-urgent patients spend their entire wait at home, an expression for the expected number of hospital bed-days per year associated with a given bridging policy was also derived. Details of this approach and illustrative results generated with parameter values estimated from retrospective data from Great Ormond Street Hospital, London, are presented elsewhere (Crowe et al. 2011). The parameter values are reproduced for ease of reference in Tables A1 and A2 in the Appendix.

2.1.1 Limitations of the birth-death queuing model; donor-recipient matching

In real life, it is not the case that any donor heart is compatible with any recipient and there are important considerations regarding weight and blood type compatibility. Current stated practice in the UK for donor-recipient matching by weight is to allow transplantation of hearts from a donor up to three times the recipient's weight but weighing no less than them. In general, matching by blood type must follow the donor-recipient ABO-compatibility rules set out in Table 1. However, newborn infants have relatively immature immune systems and low blood-group antigens, which means they may receive a heart transplant from a donor in an ABO-incompatible blood group (Irving et al. 2010; West et al. 2001).

Given that the absence of realistic donor-recipient compatibility rules in the birth-death model is an obvious deficiency, it is of interest to examine how far this absence impacts on its output metrics and hence the insights that can be drawn from these. In the remainder of the paper, we investigate the relative size of the effects of the blood type and weight matching simplifications and the extent of their combined impact on the results of the birth-death model. We do this with the motivation of better understanding the potential for using quantitative forecasts generated from the birth-death model to inform policy.

Table 1: Contingency table indicating whether a given recipient and donor are tissue matched.

	Donor blood group	**O**	**A**	**B**	**AB**
Recipient blood group	**O**	Yes	No	No	No
	A	Yes	Yes	No	No
	B	Yes	No	Yes	No
	AB	Yes	Yes	Yes	Yes

2.2 Simulation

A computer simulation model was developed in which patient and donor heart arrivals were sampled from Poisson distributions, with mean rates the same as those in the birth-death model (Table A1, Appendix). The patients were categorized according to the classes defined in the birth-death model (Figure 1) and both patients and donors were assigned to one of three weight groups (<10kg, 10-30 kg and >30kg), again using the proportions adopted in the birth-death model (Table A1, Appendix). Within the simulation, in addition to being assigned a weight band, donors and patients were assigned a 'continuous weight' sampled from a uniform distribution within their assigned weight group, i.e. from a uniform distribution for 5-10kg, 10-30kg and 30-80kg (where the lower limit of 5kg and upper limit of 80kg were assumed to be reasonable cut-off points). Donor hearts and patients were also assigned a blood type upon arrival, sampled at random with the proportions in each blood group set to those of the general UK population: O (44%), A (42%), B (10%) and AB (4%) (NHS Blood and Transplant 2011).

Upon arrival, patients were assigned an expected survival time in the absence of transplant, sampled from a negative exponential distribution with mean death rate dependent on their patient class and taking the values adopted in the birth-death model (Table A2, Appendix). As in the birth-death model, priority was given to patients on the urgent list when allocating hearts. If there was more than one suitable patient on the same waiting list then the heart was offered on a first-come-first-served basis. It was assumed that there was no prioritization between classes within the urgent list (i.e. between bridged and not-bridged urgent patients).

Four simulation scenarios were considered for the allocation of hearts in terms of donor-recipient matching, as described in Table 2. Within these scenarios, two forms of weight matching were considered. First, referred to as 'group weight matching', where there is a requirement for the donor and recipient both to have a weight within the same range from 5-10kg, 10-30kg and 30-80kg. This is the same rule assumed for the birth-death model. The second form of weight matching uses the 'continuous weight' property of recipients and donors. This form of weight matching requires the ratio of donor to recipient weight to be in the range (McMahon et al. 2003; Suddaby 1999), i.e., a heart may be offered to a patient from a donor up to three times their weight but weighing no less than the patient, which is currently the stated UK practice. Two of the simulation scenarios include blood type matching, for which donor and recipients must be ABO-compatible.

A time-slicing simulation approach (Robinson 2004) was implemented in which all simulation events (referrals of patients and heart donations, matching, deaths and transplantation) were deemed to take place at weekly intervals. Each simulation run concerned the operation of the system over a five year period, following a two year 'warm-up period' (selected using Welch's graphical method) to allow steady state to be approached. Output metrics include the average annual number of transplants and deaths per year (from either urgent and non-urgent lists), the average patient waiting time to transplant or death and the average number of bed-days used by urgent list patients. In order to estimate the mean number of bed-days per year associated with a given bridging policy, it was assumed that all urgent patients spend the

entirety of their stay in hospital, while non-urgent patients wait at home (as in the birth-death model). Results were averaged over 100 simulation runs with upper and lower 95% prediction intervals calculated using the Student's *t*-distribution (Robinson 2004). The number of runs was chosen after some initial experimentation and on the basis that the prediction intervals were adequately narrow for the purposes of this analysis. A different stream of random numbers was used in each run. The user interface of the simulation was implemented in MS Excel and the simulation engine was coded in Visual Basic for Applications (VBA).

Table 2: Donor-recipient matching criteria for the four simulation matching scenarios and the birth-death model.

Simulation scenario	Donor-recipient blood type matching criteria		Donor-recipient weight matching criteria	
	No matching	ABO-compatible	Both in same weight group (<10kg / 10-30kg / >30kg)	Current UK practice [a]
Group weight matching	X		X	
Blood type & group weight matching		X	X	
Continuous weight matching	X			X
Blood type & continuous weight matching		X		X
Birth-death queuing model	X		X	

[a] Currently in the UK, a heart may be offered to a patient from a donor up to three times their weight but weighing no less than them, i.e. donor to recipient weight ratio in range (McMahon et al. 2003; Suddaby 1999).

3 RESULTS

In total, 2400 simulation runs produced 254 966 patient and 1 221 538 donor heart arrivals. Of the total number of patients, 67.1% were transplanted and 24.5% died while waiting for a suitable heart (the remaining were still waiting at the end of the simulation). Of the donor hearts, 14.0% were used in a transplantation. The estimates for the expected waiting time to transplant or death generated are presented in Table 3 for each of the four donor-recipient matching simulation scenarios under the strategy of bridging all those patients deemed to warrant bridging.

3.1 Comparison of birth-death and simulation model

In the following, illustrative output is presented for the different simulation models and compared with the birth-death model in order to investigate how the insights from this are affected by relaxing donor-recipient matching constraints.

3.1.1 Comparing model estimates for the annual number of transplants

Firstly, we compare illustrative model results regarding the potential benefits of bridging. Figure 2 shows the mean annual number of transplants from both waiting lists (aggregated over all weight and blood type groups) as a function of the percentage of those patients warranting bridging that are bridged. The horizontal axis represents the level of bridging policy and ranges from zero to universal bridging of those patients deemed to warrant bridging.

Table 3: Simulation model estimates under different matching scenarios for the expected waiting time from referral to transplant or death, in weeks (with 95% prediction intervals). Also shown are the ratios of the expected waiting times with respect to the group weight matching scenario. These were estimated for a strategy of bridging all patients deemed to warrant bridging.

Simulation scenario	Expected waiting time from referral to transplant or death, in weeks (point estimate and 95% prediction interval)	Ratio of point estimate with respect to group weight matching scenario
Group weight matching	17.6 (16.6-18.5)	-
Blood type & group weight matching	19.5 (18.6-20.4)	1.1
Continuous weight matching	5.2 (5.0-5.5)	0.3
Blood type & continuous weight matching	7.4 (7.1-7.8)	0.4

With the birth-death model, the illustrative results show, as would be expected, a clear increase in the mean annual number of transplants as a larger proportion of those patients warranting bridging are bridged. It shows an estimated additional 0.8 transplants per year under a full bridging policy compared to a zero-bridging policy, representing an approximately 6% increase. In the group weight matching scenario, which is designed to be akin to the birth-death model, this upward trend is not discernable within 95% prediction intervals and estimates are slightly higher for the number of transplants at each level of bridging policy.

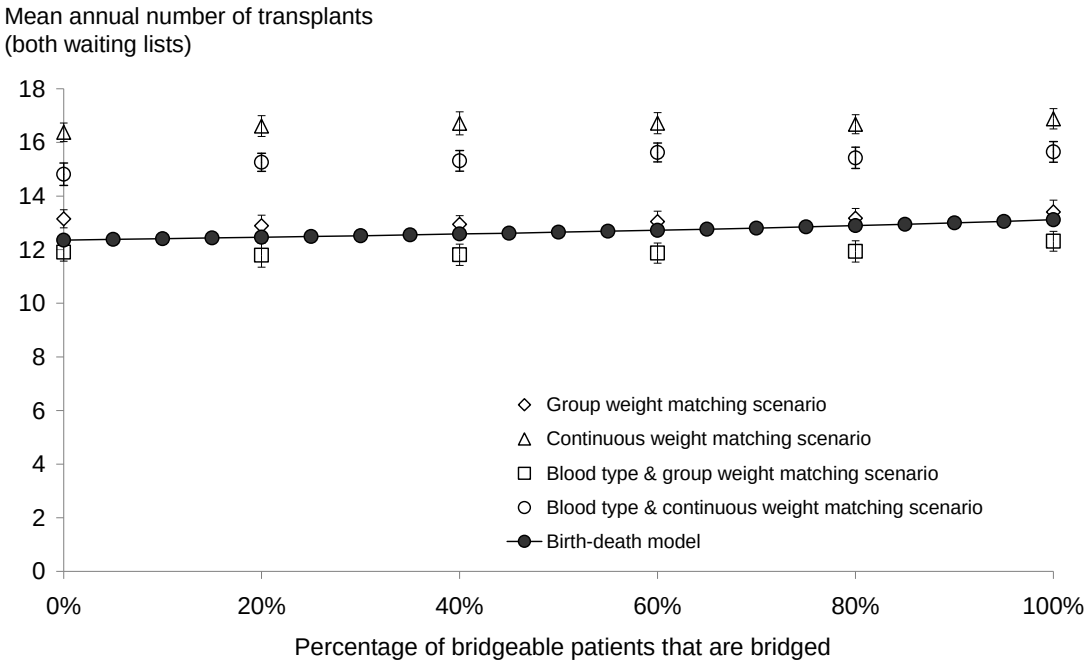

Figure 2: Model estimates under different matching scenarios for the mean annual number of transplants from both waiting lists, shown as a function of the percentage of patients warranting bridging that are bridged. Whiskers denote the 95% prediction intervals.

When more realistic matching is introduced, there is a noticeable impact (over and above the 95% prediction intervals) on the estimated number of transplants per year compared to the group weight matching scenario. When blood type matching is incorporated, the number of transplants falls by 9% on average across all bridging policies, whilst it increases by 26% for the continuous weight matching scenario. The combined impact of incorporating both blood type and continuous weight matching is an increase of 16% on average across all bridging policies (i.e. the percentage of patients deemed to warrant bridging that are bridged).

3.1.2 Comparing model estimates for the number of deaths on the non-urgent waiting list

We next compare the information derived from the birth-death and simulation models concerning the impact of bridging specifically on those patients on the non-urgent list, none of whom are bridged. Figure 3 shows the mean annual number of deaths of patients waiting on the non-urgent list as a function of bridging policy.

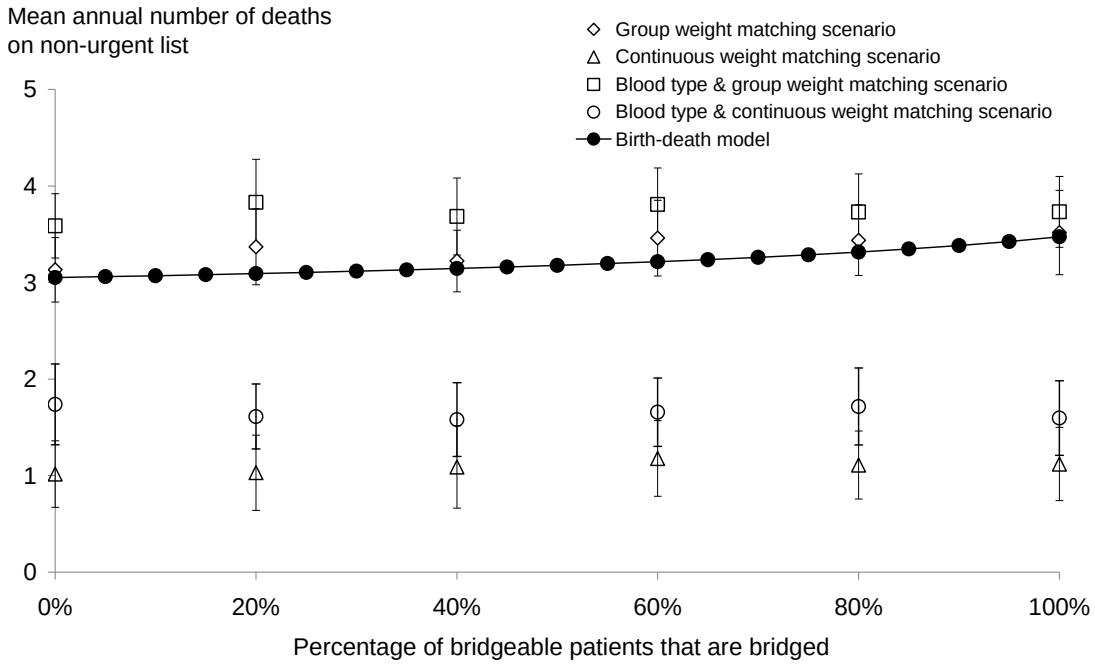

Figure 3: Model estimates under different matching scenarios for the mean annual number of deaths on the non-urgent list, shown as a function of the percentage of those patients warranting bridging that are bridged.

Using the birth-death model, the number of deaths on the non-urgent waiting list is seen to increase as bridging increases, with an estimated additional 0.4 deaths (approx. 14%) per year under a full bridging policy compared to a zero-bridging policy. Therefore, whilst bridging increases the overall number of transplants from both lists (and hence reduces overall deaths) it has a negative impact on the non-urgent waiting list. These estimates are within the 95% prediction intervals of the group weight matching simulation scenario estimates. When the donor-recipient matching simplifications are changed, the estimated number of deaths per year increases when blood type matching is incorporated (by 12% on average over all bridging policies) and decreases when continuous weight matching is incorporated (by approximately 67% on average). The combined impact of incorporating both continuous weight and blood type matching is, on average across all bridging policies, a fall of 50% in the number of deaths on the non-urgent waiting list from the scenario akin to the birth-death model.

3.1.3 Comparing model estimates for the opportunity cost of bridging

The models can be used to explore some of the wider implications of different bridging policies in terms of the scarce resources of cardiac units. Every bed-day used for an urgent heart transplant patient (bridged or not) is a bed-day that cannot be used for other patients that may need it, hence there is an opportunity cost associated with each bridging policy. Figure 4 shows the mean annual number of transplants at a given level of bridging versus the mean annual number of bed-days used for that policy (the opportunity cost). Each data point represents a bridging policy within the model, i.e. a percentage of those patients warranting bridging that are bridged.

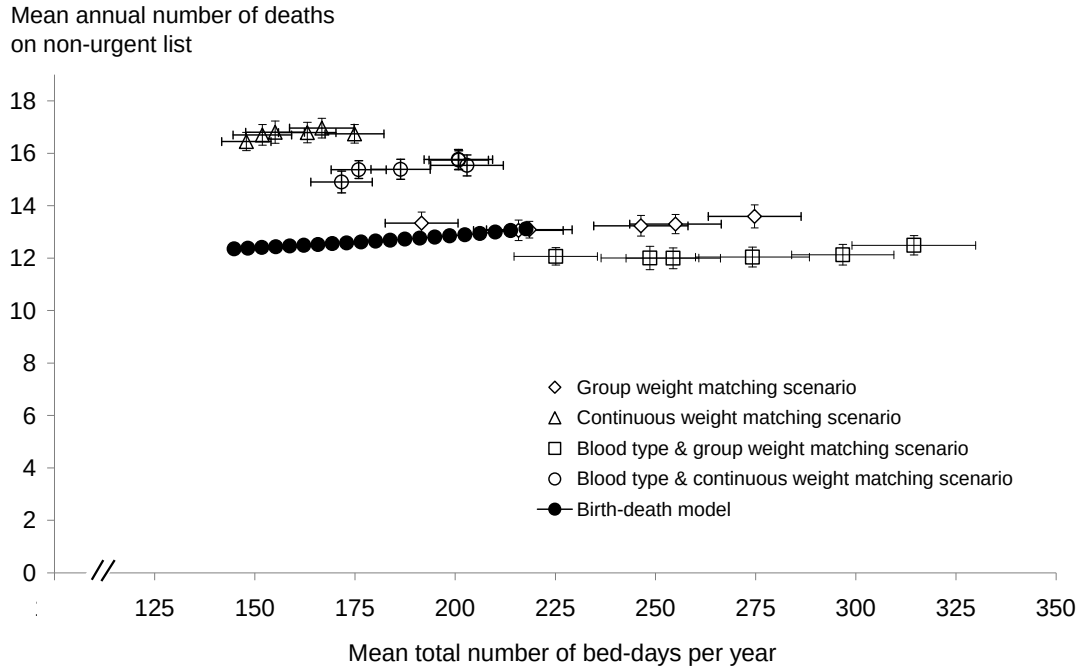

Figure 4: Model estimates under different matching scenarios for the mean annual number of transplants from both waiting lists as a function of the annual number of bed-days required to achieve that benefit.

Moving from a policy of zero bridging to one of bridging all patients deemed to warrant it, the increase of 0.8 in the annual number of transplant per year comes at an additional opportunity cost of approximately 75 bed-days according to the birth-death model. In the group weight matching simulation scenario the additional opportunity cost is approximately 80 bed-days, although the absolute number of bed-days associated with either bridging policy is higher than in the birth-death model.

When the donor-recipient matching simplifications in the group weight matching simulation scenario are relaxed, the additional opportunity cost of bridging is approximately 90, 25 and 30 bed-days for the blood type, the continuous weight, and the continuous weight and blood type matching scenarios respectively.

4 DISCUSSION

The previously developed birth-death queuing model of pediatric heart transplant waiting lists (Crowe et al. 2011) was deliberately chosen to be simple as it allowed key relationships to be explored analytically, which was appealing in a non-linear system with multiple contributing factors. Further, the queuing theory model could be solved exactly with no need for approximation. Illustrative results offered some

initial insights regarding the inter-relationships of the system that were of interest to clinicians and managers.

However, it was acknowledged that the implications of the donor-recipient matching simplifications, which were necessary for reasons of mathematical tractability, would need to be understood and potentially addressed before such a model could directly aid policy-making. The computer simulation model we subsequently developed was designed to generate the same output metrics as the birth-death model under a more flexible framework that explicitly incorporates broader donor-recipient compatibility criteria. Hence it could be used to directly investigate the impact of relaxing simplifications regarding compatibility.

Overall, we found that changing from group weight matching to more realistic continuous weight matching in the simulation led to a more appreciable (and opposing) impact on the simulation output metrics than the incorporation of blood type matching. When combined, the effects partially cancelled each other to give a relatively small (but not-negligible) net increase in transplant levels and net decreases in the number of deaths on the non-urgent list and bed-days used, suggesting a tendency toward pessimistic forecasts by the original birth-death model. This outcome cannot be generalized however, as it may depend on the nature of the matching algorithms and the values of the input parameters.

Interestingly, the group weight matching scenario, based on exactly the same assumptions as the birth-death model, did not forecast the use of bridging leading to an increase in expected annual rates of transplantations as clearly as the birth-death model does (Figure 2). Within the simulation, time is regarded as discrete and perhaps for such a discrete stochastic process, were it soluble, the increase in annual transplant rates truly is so small that it cannot be detected. Another possibility concerns the nature of the queuing theory underlying transplantation: stochastic analysis of waiting list dynamics has proved difficult because it involves extreme combinatorial complexity (Gallivan and Crowe 2011). Nevertheless, the simulation results across all scenarios do not contradict the trends established from the birth-death model.

In our simulation we sampled weights, first by sampling a weight range from 5-10, 10-30, 30-80 kg, then a weight within this range assuming a uniform distribution. While this has some computational advantages in the context of the study, simulation allows the inclusion of alternative options such as sampling from non-uniform distribution or even a continuous weight distribution over the whole range. The nature of such sampling undoubtedly has some effect on the metrics that the simulation forecasts, so it is unwise to treat these forecasts as precise. We have also assumed that both patient and donor weights are in the range 5-80 kg, which is not always the case.

The simulation results for the most realistic scenario with blood type and continuous weight matching support the insights established from the birth-death model, which is encouraging in terms of supporting the validity of insights drawn from it. In this manner, the complementary use of both analytical methods and simulation provides a means by which to understand better the validity and usefulness of modeling to inform policy decisions in this area. In future work, a combined approach such as this could also be used to assess and, if needs be, address the limitations of the birth-death model in modeling changes in patients' urgency status, weight and bridging circumstances.

5 CONCLUSIONS

We have developed a computer simulation in order to investigate aspects of the bridging to pediatric heart transplantation program within the UK. Specifically, we have used this to evaluate the implications of simplifications around donor-recipient compatibility that were integral to an existing model based on birth-death queuing theory. Although incorporating these features into the analytical model was unattainable, computer simulation allowed us to do so in a straightforward manner, both conceptually and in its implementation (coding). On the other hand, adoption of a simulation approach was not without disadvantages. There are technical issues concerning what 'warm up' period to use, how many simulation runs to perform and what time slice to adopt. Such choices may require considerable experimentation and

are thus computationally expensive and, often, require reliance on subjective opinion guided by experience. In any case, embedding a simulation model into a software tool would pose additional challenges in the implementation phase and, perhaps more importantly, in the usability of the resulting software tool.

The simulation showed a small, but non-negligible net impact on various system metrics when both blood type and weight compatibility simplifications were changed to more realistic assumptions, suggesting the original birth death model is perhaps somewhat pessimistic in its forecasts, but certainly not wildly inaccurate. However, the simulation results did not contradict the birth-death model in relation to the impact of bridging policy on the various system metrics. Although neither the analytical nor the simulation model are currently in use, we think that by engaging closely with relevant clinicians in the modelling process, we highlighted a number of key issues that are very relevant in the operation of the real life system and provided useful insights into the key relationships associated with pediatric cardiac transplant services.

Despite the individual limitations of each model, we have demonstrated that the complementary use of analytical and simulation methods provides a means by which to understand better the relationships in this problem, which could be useful in informing policy decisions in this area. Added benefits of complementary use of the two methods include the increased face validity of the models to clinicians and the increased confidence of the analytical team in the results. On the other hand, longer study development and execution times, limited availability of analytical and programming expertise, and increased computational complexity may dissuade the complementary use of the two methods.

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A APPENDIX

The input parameter values of the birth-death model shown in Tables A1 and A2 were estimated from retrospective data for patients at Great Ormond Street Hospital, as described elsewhere (Crowe et al. 2011). These parameter values were also used within the simulation model.

Table A1: Mean arrival rates of donor hearts and patients and the proportions in each patient class (by weight group).

Weight group	Mean patient arrival rate (per year)	Proportion of patients on urgent waiting list	Proportion of patients on urgent list that are deemed to warrant bridging	Mean donor heart arrival rate (per year)
≤10kg	6.6	0.43	0.32	2.5
10-30kg	7.35	0.37	0.56	5.2
≥30kg	6.6	0.5	0.55	94.3

Table A2: Mean annual death rates on the waiting list of patients by class (by weight group).

Weight group	Death rate on waiting list (per year)			
	Non-urgent list patients	Urgent bridged patients	Urgent patients warranting bridging that are not bridged	Urgent patients not warranting bridging
≤10kg	0.9	8.1	26	10.4

10-30kg	0.4	3.7	26	4.7
≥30kg	0.9	8.4	26	10.8

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