Proceedings of the 2000 Winter Simulation Conference
J. A. Joines, R. R. Barton, K. Kang, and P. A. Fishwick, eds.

USING SIMULATION FOR THE ECONOMIC EVALUATION OF LIVER TRANSPLANTATION

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ABSTRACT

This paper demonstrates the use of simulation in an evaluative study for the technology of liver transplantation from cost-effectiveness point of view. This study is conducted in the United Kingdom where there are no explicit guidelines for the prioritization of patients waiting for transplantation. Another objective of the model is to enable health economists to understand the technology of liver transplantation and evaluate alternative policies for prioritizing patients in the waiting list. The paper shows the construction of a tailor-made package (LiverSim) and provides an example of how this package is used by the stakeholders to assist in the evaluation process. Some final lessons are drawn that simulation helps in exploring more issues outside the boundaries of quantitative results.

1 INTRODUCTION

The ability needed to carry out successful liver transplants has improved rapidly within the last two decades, and it is therefore not surprising to find that numbers of such transplants have increased. In 1980, fewer than 50 liver transplants were performed throughout Europe (Neuberger and Lucey 1994), yet in 1997 over 600 liver transplants were performed in England and Wales alone (HERG 1998). As a consequence of the increased the numbers of liver transplants now being carried out, the waiting list for liver transplants has similarly increased considerably during this period. Although it is clearly beneficial that more people are having this life-saving operation, the increase and success of transplantation is dependent on having enough donor organs. Unfortunately for those needing such transplants, the supply of donor organs has remained relatively constant over recent years. This is in spite of the increased use of split liver transplantation, which allows one donor organ to be used for two smaller recipients, and the fact that there are more livers from donors classified as marginal, for example non-heart beating donors and those over 60 years of age. Unfortunately, as a result of the shortage of donor organs, a substantial minority of patients on the transplant waiting list die before a donor liver becomes available (Neuberger 1997).

There has never been a formal study to examine the efficiency of liver transplantation. However, there is a growing body of evidence to suggest that for certain types of liver diseases, transplantation offers improved survival for the individual recipient (Bryan et al 1998, McMaster and Dousset 1992). In contrast, no evaluative study has yet been carried out in order to consider the potential influence of the liver transplantation selection policy that a particular liver transplant unit, or center, has upon the long term survival of patients with end stage liver disease. Nor has there been any study of the impact of such changes in survival in influencing decision-making with regard to the overall cost-effectiveness of this technology. This study has applied a simulation modeling approach to address these issues at the liver transplant unit at the Royal Free hospital in inner London; a region of the UK. It should be noted that the UK is divided into seven transplant regions, with each being managed by a central hospital. The Royal Free hospital is a central hospital for the northern half of Southeast England. There are two central issues addressed in this study. One, the use of simulation modeling to provide an understanding about the cost-effectiveness of liver transplantation surgery. Two, the use of simulation modeling for evaluating alternative prioritization criteria measured by cost-effectiveness.

Each country, or indeed unit or center, may have different policies in place that help in drawing up the list of patients and thus who should take priority. The United States has a formal point system in place which allocates donor liver grafts based upon the medical status of the patient. This means that those patients who are considered in worse health are considered a higher priority. Other factors involved are blood type compatibility with the donor organ and the length of time already spent waiting (Pritsker 1998). Patients are re-ranked on the list each time

a new donor liver arrives. Unlike the United States, the UK has no formal criteria for the allocation of donor liver grafts. The UK has a public, government-funded healthcare system, and this is known as the National Health Service (NHS). Those working in liver transplant units or centers in the NHS in the UK are broadly in agreement that all patients on the liver transplant waiting list will be considered. However, as there are no formally-agreed policies or statements about how priorities on waiting lists should be decided on, it is therefore all the more important that those involved are made aware of all the factors that complicate their decisions. Rather than looking at how ill a patient is, length of time on the waiting list seems to be a dominant prioritization criterion in the UK.

In a review of the criteria for prioritization of patients on the waiting list for transplantation of all solid organs, Jonasson (1989) argues that "Length of time on the waiting list is the least fair, most easily manipulated and most mindless of all methods of organ allocation". This is mainly because, as the period on the waiting list is extended, the health of the patient tends to deteriorate. Traditionally, such patients are given the highest priority based on the fact that they have waited for the longest period of time and they may not otherwise survive. However, from the point of view of fairness or even cost-effectiveness, this policy may not be optimal since such patients tend to have a lower rate of success than that of less severely ill patients who have been waiting for a shorter time period. Given the importance, in the UK at least, placed on the length of time on the waiting list, as well as other factors that complicate the decision-making process, it is clear that it is timely to look more closely at issues concerning prioritization on waiting lists such as those for liver transplantation.

2 THE NEED FOR SIMULATION MODELLING

From the above discussion it can be seen that it is important to find methods for prioritizing patients that are considered fair by all parties involved in the process. To achieve such an objective is, it can be argued, impossible, as 'fairness' cannot be measured quantitatively, and there can therefore be no absolute definition of 'fair'. For example, it might be thought to be fair to give priority to the sickest patients with a relatively smaller survival prognosis, yet it might equally be argued that it is instead fair to give priority to less sick patients but who have a higher survival prognosis. There can be no single 'right' answer as to which patient is deserving of being higher up the priority list; it depends on the particular situation and the circumstances faced by the decision makers, and on the factors that contribute to the process. What is needed, then, is a tool that enables those involved to explore different policies for prioritizing the waiting list and their likely impact on the system and involved stakeholders.

The technology of liver transplantation for the treatment of end stage liver disease represents a complex clinical situation which changes over time. Analytical approaches such as decision trees and Markov modeling (Roberts 1992) may fall short of giving a reliable picture of the situation, particularly given its many complicated features. Discrete Event Simulation (DES), however, represents a stronger candidate (Baldwin et al 1999) in that it offers the ability to explore aggregate and individual levels of a system. It also offers higher level of transparency as it follows individual entities throughout the process.

3 THE LIVERSIM MODEL

A simulation package (LiverSim) has been built and tailored in order to enable stakeholders to understand the situation and experiment with different policies with regard to prioritization of patients in the waiting list. The model is applied to patients waiting for transplantation with two main types of liver disease: alcoholic liver disease (ALD) and primary biliary cirrhosis (PBC). There are two reasons for choosing these two diseases. First, patients with these diseases represent the majority of liver transplants currently undertaken in the Royal Free Hospital transplant center and more generally in the UK (O'Grady and Williams 1993). Second, several published and validated prognostic indices are available for these diseases which can be used to predict survival in the absence of transplantation given the values of the clinical variables specified (Anand et al 1997, Hughes et al 1992, Dickson et al 1989).

The final output measures are divided into two classes. First, identify the cost-effectiveness of liver transplantation against no transplantation. Second, identify the cost-effectiveness of the alternative policies for prioritization of patients in the waiting list. Hence, the structural development of a simulation model should reflect the patterns of care received by patients referred for liver transplantation and of a subsidiary model reflecting the patterns of care received by patients receiving treatment (other than transplantation) for liver disease.

3.1 Background of the System

All patients enter the system with end stage liver disease (ALD or PBC). Each patient is then assessed in order to determine his or her suitability for transplantation. If the patient is selected for transplantation then he/she joins the waiting list for transplantation. Patients are classified as either routine or super urgent. However, super urgent patients are not considered in this model. First, due to the severity of their condition, super urgent patients are relatively inflexible in the timing and prioritization for transplantation. Typically, such patients will die within three or four days if a donor liver is not made available. Second, super urgent patients generally receive very different

patterns of care from routine patients, both in terms of the quantity and type of resources used and in terms of the timing of treatments administered. For routine patients waiting at home, the advent of complications may mean that hospital in-patient admission(s) are required. If a suitable donor organ becomes available, the patient is transplanted. If the patient survives the peri-operative period, he/she may survive without developing complications. The patient may develop complications post-transplant that require either one or a series of post transplant admissions to hospital. The patient may require re-transplantation (and hence loop back through the system to the assessment stage) or die at any time as a result of graft failure. If the patient is rejected for transplantation, then the control is for the pattern of care for patients receiving treatment for their on-going liver disease. This structure is far less complex than that for patients going forward for transplantation (see Figure 2). Patients with liver disease require constant monitoring through regular outpatient visits and may develop complications which require in-patient admission(s). As in the transplantation system, patients enter the system with end stage liver disease with ALD or PBC.

3.2 The Model's Structure

The computer model for LiverSim was built using Simul8 and Visual Basic. The Simul8 model provides a general description of the physical layout of the system. It is also responsible for the simulation engine, while Visual Basic is used for developing an interface for input/output processing and what-if experimentation. The model is divided into two separate structures; the transplanted structure and the non-transplanted structure. Both structures are run simultaneously for comparison purposes. Figure 1 shows the liver transplantation structure while Figure 2 shows the liver disease structure. In Figure 1, all states for patients before the transplantation phase are either parts of the assessment phase or the candidacy phase. On the other hand, states after transplantation belong to the post-transplantation phase. Naturally, 'death' is the last event in the system and all entities are supposed to end there. Notice that some patients may die before they are transplanted as the model makes room for the assumption that some patients may die while they are waiting for transplantation as results of various reasons. Patients at the candidacy phase are either waiting at home "Candidacy", in the hospital for complication "Candidacy Admission" or with severe complication in the "ITU". When a liver becomes available, all of them will be considered to determine the best match for it. There are also some logical "bins" located in some parts of the screen and those represent termination of entities from the model. For example, the first bin from the left receives the patients who would arrive to the model after the maximum number of recruited patients is reached. The second bin is for livers that are rejected, this is used to model livers for which there are no matches. The structure of the model requires patients to be prioritized and selected instantly for transplantation, however, that was not technically possible in Simul8. To cope with this, selected patients had to be cloned, the original clone is sent to the third bin, while the new clone is sent to the transplantation. Table 1 explains of the different nodes in Figures 1 and 2.

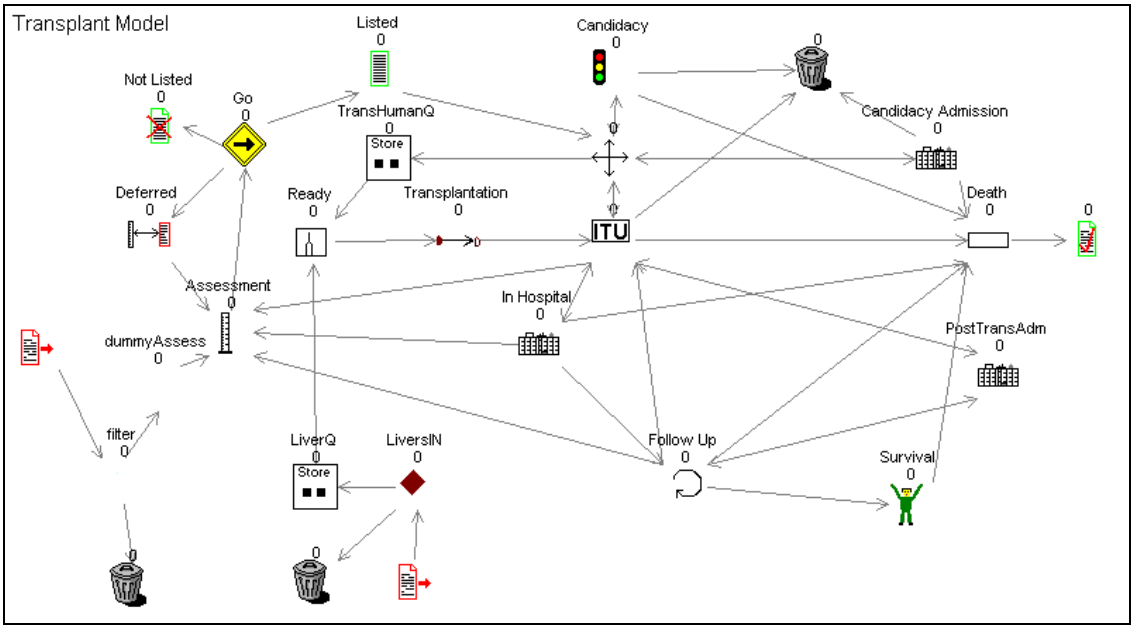

Figure 1: Simul8 Representation of the Liver Transplantation Model

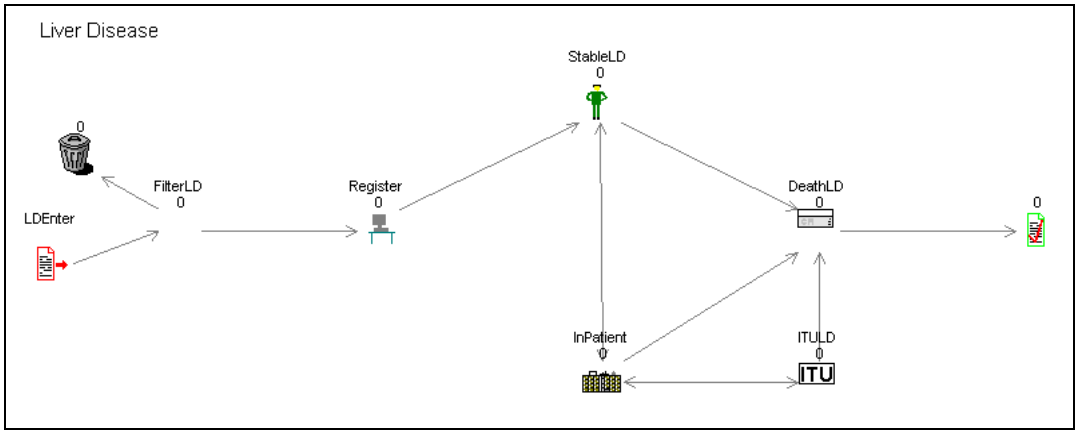

Figure 2: Simul8 Representation of the Liver Disease Model

Table 1: Details of Simul8 Representation of the LiverSim Model

DummyAssess	A logical point for establishing patients' individual properties
Assessment	Assess patients' suitability for transplant
Go	To distribute patients based on assessment results
Deferred	Deferring transplant decision
Listed	Listing for transplant
Candidacy Admission	Hospital admission during candidacy phase
Candidacy	A patient being at candidacy phase in a stable state
Transplantation	The transplantation procedure
Not Listed	Rejected from transplantation
PostTransAdm	Hospital admission after transplantation
Follow Up	Two years medical follow up after transplantation
Survival	Being alive after the follow up period
LiverQ	Logic state for searching for the best match
In Hospital	Being in the hospital after the transplantation procedure
ITU	Intensive care unit
LiversIN	The point where livers enter the system
TransHumanQ	Where the best matched is transferred from the waiting list
LDEnter	The point where liver disease patients enter the model
Register	Registered as being liver disease patient
StableLD	A liver disease patient at a stable state
InPatient	In-patient hospital admission
ITULD	Intensive care for liver disease patients
Filter	Stopping extra patients from entering the system

4 THE MODEL'S DETAILS

This section gives more detail about LiverSim in terms of input variables, output representations, and facilities for experimentation.

4.1 Inputs to the Model

Input variables for LiverSim vary from identifying the patient type, length of stay, resources and costs to probabilities of tests and treatments. Input facilities are developed in the same way as for the ABCSim package (Baldwin et al 1999). Figure 3 provides an example of how inputs variables are entered in the LiverSim model.

Table 2 and Table 3 present the input variables associated with both the liver transplantation and the liver disease model. The sign [£] indicates that there is a cost associated with the variables, for example, 'length of stay' in a hospital. These costs are assigned as per each unit, for example for the 'length of stay' costs are per day, whilst for drugs costs are per unit of drugs or per session in case of, for example, physiotherapy sessions. Some variables, such as specific assessment tests have lump sum costs. In Table 2 the severity group means that all patients are divided into four groups where 'group A' represents patients with the least severe liver disease and 'group D' represent patients with the severest liver disease. The reason for having some of the input variables depending on

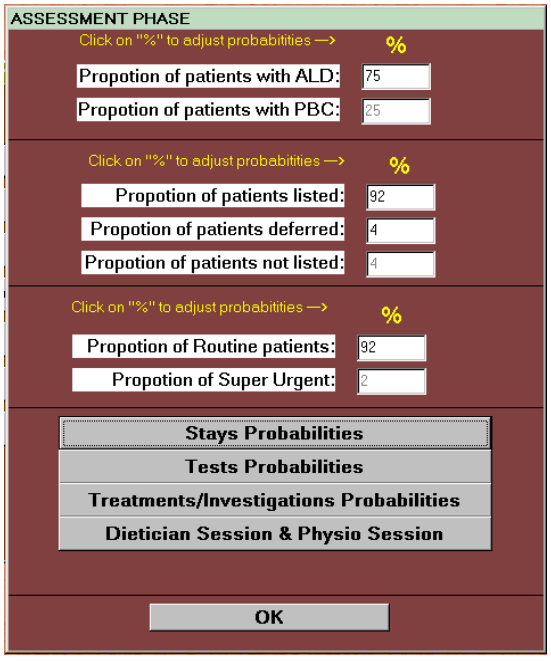

Figure 3: Input Window in the LiverSim Model

the group is because each group may require different types or amounts of treatment.

4.2 Outputs from the Model

Average life years and average costs are calculated for both the transplant process and the non-transplant process. The average life for the liver transplantation model is calculated after the point of transplantation, whilst the average life for patients in the liver disease model is calculated from the point of registration. Average cost for either model is calculated from the point where the patient enters the model. Stakeholders are able to take these results for analysis in spreadsheets for comparisons with other runs or configurations of the model.

5 PRIORITIZATION CRITERIA

As mentioned above, one of the main objectives of this model is to facilitate the economic evaluation of different prioritization criteria for patients on the waiting list. This is an important issue in the modeling process as it represents a dialogue between the involved stakeholders for identifying the most suitable selection policy. The alternative proposed criteria are discussed below. Obviously these policies are applied for matched (suitable) patients only. The two main matching criteria currently used throughout UK liver trans-plantation centers are the blood group compatibility and body weight of the donor and the recipient, the body weight acting as an indicator of the size of the donated liver. Any selection strategy employed in the model is constrained by

Table 2: Input Variables for the Liver Transplantation

Assessment phase
Assessed with (PBC or ALD)
Listed patients (listed, deferred, rejected)
Severity groups (A, B, C, D)
Length of stay based on groups [£]
Assessment out-patient visits: no. of visits (0,1,2,3) [£]
Investigations and tests in:based on groups [£]
Physiotherapy sessions in assessment phase (1, 2 or more sessions): probabilities based on groups [£]
Dietician sessions: assessment phase (1,2,3: sessions) [£]
Length of time between end of assessment and listing: probabilities based on groups
Candidacy Phase
Probability of candidacy admission (PBC, ALD)
Inter-candidacy admissions
Candidacy admission length of stay [£]
Transplant phase
Length of stay in transplant phase [£]
Length of transplant operation [£]
Investigations and tests in transplant phase: probabilities based on groups [£]
Drugs in transplant phase: based on groups [£]
Physiotherapy sessions in transplant phase [£]
Dietician sessions in transplant phase [£]
Post-Transplant phase
Probability of one or more post-transplant admission [£]
Frequency of post-transplant admissions
Post-transplant admission length of stay [£]
Investigations and tests during post-transplant admission: probabilities based on groups [£]
Proportion of patients re-transplanted (PBC, ALD)
Out-patient visits in follow up phase [£]
Investigations at follow-up phase: based on groups [£]
Drugs in follow up phase: probabilities on groups [£]
Drugs during post-transplant admission: probabilities based on groups [£]

Table 3: Input Variables for the Liver Disease Model

Probability of patients with PBC or ALD
Length of time between admissions
Length of stay for admission reasons [£]: Ascites Malnutrition Hepatocellular carcinoma Sepsis including SPB GI bleeding varices GI bleeding non varices Hepatic encephalopathy Electroylte abnormalities Alcohol withdrawal Liver failure
Frequency of out-patient visits annually [£]

the frequency of the supply of donor liver grafts and the need to ensure that all donor liver grafts allocated are matched accordingly. Once patients are matched and classified to be suitable for transplant, selection criteria are used to prioritize these patients. Selection criteria in Table 4 were chosen for evaluation by the research team of health economists, in collaboration with clinical colleagues at the hospital center where the project was based.

The evaluation process is based on their incremental cost-effectiveness ratios. Incremental costs were defined in terms of the total costs with transplantation minus total costs without transplantation, and incremental effectiveness was defined in terms of life years gained with transplantation minus life years gained without transplantation.

The 'High wait' selection policy represents the reference policy for comparative purposes since this policy represents the system that presently operates most commonly throughout the UK for routine patients. The 'Low wait' policy represents the reverse of the current one. For the 'High PI' and 'Low PI' selection policies, clinical severity was defined in terms of prognostic indices without transplant at the time of listing with patients with a poorer prognosis defined as more clinically severe than patients with a better prognosis. For the final selection policy, patients were first ranked in order of clinical severity as previously defined and then placed in one of four groups (A, B, C or D) where 'group D' represented the most clinically severe group. Patients in 'group D' were then given a lower priority for a donor organ than patients in 'groups A, B or C'. As the selection criteria are changed, the order and/or timing of transplantation for the cohort of patients is changed. The impact of such changes upon the estimated net life expectancy, average net costs and overall cost-effectiveness of the transplantation program is investigated. The simulation models primarily use a lifetime of ten years in total with a five-year recruitment and a five-year follow up period for all patients.

6 AN EXAMPLE OF USE

The main objective of modeling is to facilitate experimentation for stakeholders for evaluating the different policies. This section presents an example of how results and analysis are conducted by stakeholders. This particular example is based on data from the Royal Free Hospital. Results for both the transplanted model and the non-transplanted model are presented for comparison. Table 5 shows the summary simulation results for the base case analysis which assumes a cohort of 1000 patients entering the model. In Table 5 'costtx' and 'costld' are expected costs for transplanted and non-transplanted patients respectively, whilst 'survtx' and 'survld' denote expected survival for transplanted and non-transplanted patients respectively. The reference selection policy, 'High wait', gives an expected total cost per patient transplanted over the ten years of £59,086 (CI: £52,361 – £66545), where future costs are discounted at 6%, with an expected post-transplant survival time of 4.12 years (CI: 3.03 – 4.99 years). The expected total discounted cost per patient not transplanted over the same time period is £24,185 (CI: £19029 – £29834), with an expected survival time of 1.1 years (CI: 0.94 – 1.21 years).

The ICER for the reference selection policy is £11,557 (1999 prices). This estimate can be compared with the ICER generated using alternative selection policies. The results in Table 5 shows that the ICER's associated with 'Low wait', 'High age', 'High PI', and 'Low PI' policies are all higher than the reference selection policy. Whilst, the ICER associated with 'Low age' is £10424 and the ICER associated with 'Groups' is £9077, both of which are lower than the reference policy. Therefore, these results indicate that the overall cost-effectiveness associated with policies where younger patients are given priority, and selection on the basis of clinical severity groupings (where the most severely ill patients are given lower priority)

Table 4: Selection Criteria for Transplantation

High wait	Patients on the waiting list in order of highest time spent waiting
Low wait	Patients on the waiting list in order of lowest time spent waiting
High age	Patients on the waiting list in order of highest age at time of listing
Low age	Patients on the waiting list in order of lowest age at time of listing
High PI	Patients on the waiting list in order of highest clinical severity
Low PI	Patients on the waiting list in order of lowest clinical severity
Groups	Patients on the waiting list by clinical severity groupings

Table 5: Base case results: (1000 patients)

Policy	Costtx (£)	Costld (£)	Survtx (yrs)	Survld (yrs)	ICER (£)
High wait	59086	24185	4.12	1.1	11557
Low wait	57667	22686	3.97	1.01	11818
High age	54725	16907	4.07	0.96	12160
Low age	57382	25694	4.18	1.14	10424
High PI	57613	18952	4.26	1.03	11969
Low PI	59520	24078	4.09	1.14	12014
Groups	59100	32777	4.02	1.12	09077

would result in improved cost-effectiveness relative to the reference selection policy.

7 CONCLUSIONS

The paper has described the development of LiverSim, which is a simulation tailor-made package for the purpose of the economic evaluation of the process of liver transplantation and the evaluation of alternative prioritization criteria for waiting lists. The use of simulation modeling has proved to offer a high level of precision in terms of outputs, as has been demonstrated by the case study presented. However, in the case of liver transplantation it is important to bear in mind that 'output', that is, which patient will be at the top of the waiting list is not merely a matter of inputting some data, pressing a button and wait for the 'right' answer. Indeed, there cannot be a 'right' answer. Such decisions impact the quality and duration of patients' lives. Or, more precisely, a longer, or shorter, life. However, in reality such decisions are made not by patients themselves but by various stakeholders in healthcare. LiverSim is not just intended to be a tool that can solve the liver allocation problem, but can also enable those involved to better understand the issues involved. With LiverSim, stakeholders in healthcare have at their disposal a tool that they can use to aid in selecting a specific prioritization criterion. This naturally raises questions about which criteria should be used in any such selection, particularly given the ethical dimensions of liver transplantation.

LiverSim provides a tool that enables those involved to argue their case through the model. This is particularly important, for clinicians, as it is this group of stakeholders who have to sit down with the patient and explain their placement on the priority list. LiverSim allow clinicians to be alert to the various interrelated factors and to be involved as fully as is possible in the decision-making process so that they can subsequently provide a thorough, reasoned response to their patients. They may or may not agree with the decision but they can choose to present the factors that complicate the process that led to the decision. Using LiverSim also provides a means of ongoing training and development in that discussions or arguments made during the process allow for alternative perspectives on a wide range of diverse issues, many of which extend beyond the decision itself. These might involve personal and local issues such as how to handle feedback to patients, or involve issues of a more general or global nature such as to how to ensure that more people donate their organs and how that might best be done.

One final lesson learned from the LiverSim experience is that as the number of liver transplants performed in the UK continues to increase, the calls for explicit guidelines for prioritizing patients on the waiting list are likely to escalate in the future. DES may prove to be a powerful tool in assessing the impact of alternative selection strategies for transplantation – not just based on cost-effectiveness but also on quality of life measures as well. It may also prove to be useful in facilitating the timing of other surgical interventions and in healthcare decision-making more generally, particularly in light of the fast pace of change in healthcare today.

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