

NHS BLOOD AND TRANSPLANT

DEVELOPMENT OF A LIVER TRANSPLANT ALLOCATION SCHEME (LTAS)

AN ALLOCATION PROCEDURE BASED ON TRANSPLANT BENEFIT

1 Introduction

A new procedure for the allocation of livers is being formulated. It is intended that a number of potential allocation systems will be tested in a simulation process against the current ad hoc unit based allocation process. The options include a needs based allocation, based on risk of death on the transplant list, and one based on transplant benefit- the net gain in life years obtained by transplantation. This document summarises the statistical work that is associated with the development of this allocation procedure; it will be regularly updated.

2 Metric for summarising benefit

Benefit may be measured in a number of ways, including the estimated difference in one or five year survival rates with and without the transplant, the difference in median survival times, and the difference in expected life time over a given time period. The metric that we have chosen to use is the estimated difference in expected life time over a five year period. This can be estimated from the area under a survivor function to five years. Cox regression models are to be adopted for survival times, and so the estimated survivor function is a step function. The area under this estimate is then easily obtained by summing the areas of a number of rectangles.

3 Transplant benefit model

The main components of a transplant benefit model are as follows.

- (i) A model for the survival of an individual from the time that a donor organ becomes available if that individual does not receive a transplant. This is termed *survival on the transplant list*.
- (ii) A model for the survival of an individual from the time that a donor organ becomes available if that individual does receive the organ. This is termed *transplant survival*.

3.1 Modelling survival on the transplant list

A Cox regression model is used to model the time from when an organ becomes available to death on the transplant list. The model will be developed using the data from patients registered for a transplant between 1 April 2003 and 30 June 2009 and will incorporate the following factors:

UKELD as time dependent variable, slope of UKELD from registration to most recent value, BMI, age, gender, ethnicity, aetiology, prior transplantation and previous time on transplant list.

Qu1: Is it UKELD or the components of UKELD that should be considered in the modelling process? If it is the components of UKELD then it will be these and the slopes of these that will be considered in the modelling process.

Qu2: Should transplant centre be considered as a factor in the modelling process?

Data for the patient factors diabetes, patient status (respiratory support/ITU/hosp/home), renal support and prior cardiac disease have only been collected since 1 September 2007. Once a model has been developed based on the full dataset, this model will then be applied to a subset of data comprising patients registered for a transplant from 1 September 2007 to 30 June 2009. The additional factors will then be incorporated in to the model to see if they have an effect on survival on the transplant list.

Initially, simulation models (see Section 6) will only be possible for the factors in the model fitted to data from 1 April 2003. This could later be updated to include the additional factors once a sufficiently large follow-up period is available.

3.2 *Informative Censoring*

In modelling the time from registration to death, patients who are removed from the list because of a deteriorating condition will be regarded as events. Patients who are removed for other reasons contribute censored survival times. Those who receive a transplant at a given time also contribute a censored survival time. Since patients often deteriorate while waiting for a transplant, the time to transplant cannot be assumed to be independent of the time to death on the list. The censored time of transplant may therefore be informative.

The extent of this informative censoring will be investigated and taken account of in the modelling process in the manner described below.

3.2.1 Sensitivity to informative censoring

To determine the extent of any informative censoring, a sensitivity analysis along the lines of Siannis, Copas and Lu (2005) will be implemented. Essentially this procedure introduces a parameter, δ , that reflects the extent of any association between the time to transplant and time to death on the transplant list, with $\delta = 0$ corresponding to non-informative censoring. We can then quantify how the magnitude of this parameter affects the estimates of parameters in the survival model, and hence quantities such as the median survival time. If the median is sensitive to small increases in the value of δ , this indicates that an analysis that does not take account of informative censoring may be misleading. The method as originally proposed is based on the assumption of a Weibull distribution for the time to transplant (censoring) and the time to death. However, a more flexible approach has been developed by Natalie

Staplin, an NHSBT funded PhD Student, University of Southampton, that uses piecewise exponential models for the underlying hazard functions.

This procedure will be implemented to determine the extent of informative censoring, and hence whether this needs to be taken account of in the modelling process. A preliminary analysis suggests that time of transplant is informative about time of death.

3.2.2 Modelling informatively censored data

The method used to model survival times with informative censoring is based on the procedure described in Robins and Finkelstein (2000) and used by Schaubel et al. (2009) in modelling patient survival while awaiting liver transplantation in the US. In summary, a model is developed for the probability of a transplant after time t , p_t , and a time varying weight is applied to each patient where the weight is $1/(1 - p_t)$. The effect of this is to give greater weight to those parts of the registration period where the probability of a transplant is high. For such patients, the time to death is likely to be censored by the occurrence of a transplant and so their time to transplant may not be much less than the time to death would have been. On the other hand a patient on the transplant list who in some time period has a small probability of a transplant will have a weight close to unity in this period. For this patient, the time to death is likely to be much longer than the time to transplant and so there will be a correspondingly greater period of time at risk of death. This weighting process therefore provides a way of adjusting for the association between time of transplant and time of death on the list.

In fitting this model using software packages such as SAS, it is convenient to use the counting process format for time dependent variables. Then, for any one patient the weights can be varied over the time period from registration to the earlier of time of transplant, removal from the list, or death. The values of time varying covariates such as the UKELD score or its components are incorporated into the model in the same manner.

3.2.3 Modelling the probability of a transplant

A Cox regression model will be used to model the time from registration to transplant for a cohort of patients who were registered between 1 April 2003 and 30 June 2009. The factors to be included in the model are as follows:

UKELD as time dependent variable, slope of UKELD from registration to most recent recorded value, BMI, age, gender, ethnicity, aetiology, prior transplantation and previous time on transplant list.

This model can then be used to estimate the probability that an individual with given characteristics receives a transplant after any given time. These estimates lead to the weights needed to account

for informative censoring in the model for survival time on the transplant list.

Because updated values of UKELD are not available, the slope of the trajectory of UKELD values will need to be estimated. A method for doing this is outlined in Section 5.

3.3 *Modelling transplant survival*

A Cox regression model will be used to model the time from transplantation to the earlier of death or failure of the graft. The model will be based on patients who were transplanted in the period from 1 January 2000 to 31 December 2008. Both recipient and donor factors will be included in the model.

Recipient factors: age at transplant, BMI, gender, ethnicity, aetiology, UKELD at transplant, potassium, albumin, patient status (respiratory support/ITU/hosp/home), renal support, prior transplantation and previous time on transplant list.

Donor factors: BMI/abdominal girth, age at time of death, diabetes, type of graft (whole/reduced/split), ethnicity, whether or not the donor is a donor after cardiac death and donor travel time from donor hospital to recipient centre (a surrogate for cold ischaemic time).

Interactions: Donor age and recipient HCV, and donor diabetes and recipient HCV.

Note: Recipient diabetes and prior cardiac disease have only been recorded on the elective liver registration form since 1 September 2007 so these factors will not be considered in the modelling process.

4 **Determination of transplant benefit**

At any given time when a donor organ becomes available, the pool of potential recipients will be determined according to blood group compatibility.

Qu3: Should the pool of potential recipients be determined according to blood group compatibility alone, or blood group compatibility and size? If the latter, then how should size be quantified and what are the matching criteria?

For each patient, the expected life time over a five year period will be estimated from the survivor functions for the time of survival with and without a transplant. The organ would then be allocated to the person who has the largest gain in expected life time.

Qu4: How do we handle exceptions in the analysis eg HCC and Appeals Panel patients? If additional UKELD points are to be awarded to these patient types then this will involve adjusting the estimates of survival on the transplant list for these patient types. Note that this is more difficult if the UKELD components rather than the UKELD score are included in the model.

5 Some aspects of the modelling process

In the modelling process, we will consider spline models or fractional polynomials for continuous variables.

The treatment of missing values will depend on the extent of the “missingness” amongst the factors being considered for inclusion in the model. If there are a relatively small number of missing values then a complete case analysis will be carried out. However, if the number and pattern of missing values renders this inappropriate, a multiple imputation procedure for arbitrary missing data will be adopted.

UKELD will be considered to be a time dependent variable. Unfortunately, values of UKELD between registration and transplantation will not be available. We will therefore proceed as follows.

For data from the cohort registered between 1 April 2003 and 30 June 2009, the slope of UKELD over time will be calculated from:

$$\text{Slope} = \frac{\text{UKELD at transplantation} - \text{UKELD at registration}}{\text{days from registration to transplantation}}$$

Assuming linearity, the value of UKELD at time d days after registration can then be estimated from:

$$\text{UKELD at registration} + \text{slope} \times d$$

To mimic proposed arrangements, a value of UKELD will be simulated at the start of each month following registration.

Data on intermediate UKELD values may be available from a particular centre. This can then be used to validate the assumed model, and if necessary identify an alternative functional form for the relationship between UKELD and time.

Because the slope will depend on patient characteristics and the UKELD value at transplantation will not be known in practice, a general linear model will be fitted to data on the slopes using patients registered in the period from 1 April 2003 to 30 June 2009 who were subsequently transplanted. The variables to be considered for inclusion in this model are:

UKELD at registration, BMI, age, gender, ethnicity, aetiology and prior transplantation.

The fitted model for the observed slope will enable a UKELD value to be simulated for a patient with given characteristics at any time. Since it is unrealistic to expect a reduction in UKELD score over the registration period, negative estimates of slope will be taken to be zero, which amounts to assuming that for such a patient, UKELD remains constant.

Once updated values of UKELD are being obtained on a regular basis (eg monthly) for all patients on the transplant list, the model due to Davidian and Tsiatis (2001)

will enable the actual UKELD values to be taken account of. Moreover, the availability of such data will enable a shadow allocation scheme to be put in place so that the procedure can be compared directly to the current allocation scheme.

5.1 Model checking

The adequacy of models will be examined using plots of Cox-Snell residuals, martingale residuals and Schoenfeld residuals. The likelihood displacement diagnostic will be used to identify influential observations. The validity of the proportional hazards assumption will be assessed using the method described in May and Hosmer (1998).

Many authors, including Schaubel et al. (2009), use a concordance statistic originally proposed by Harrell to summarise a model's predictive ability. However, this statistic is sensitive to the level of censoring in a data set, and moreover is not a consistent estimate. The Gönan and Heller statistic (Gönan and Heller, 2005) overcomes these problems, and so we will use this statistic to estimate concordance between observed and predicted survival times.

5.2 Use of cross-sectional data

Since any allocation rule is applied to cross-sections of patients registered on a given date, Schaubel et al (2009) recommend using cross sectional data in modelling survival on the transplant list without a transplant. We therefore propose basing the model on all patients registered on 1 April 2003, 1 October 2003, 1 April 2004, 1 October 2004 etc.

When patients who are in two or more consecutive cross sections, the earlier records will be excluded, so as to incorporate long waiters.

The resulting model will be compared with that obtained from fitting a model to time from registration until death, as a form of sensitivity analysis.

6 Simulation of allocation procedure

To determine the properties of an allocation process based on transplant benefit, including the characteristics of patients that have been allocated organs, and estimated survival following transplantation, a simulation scheme will be adopted.

We start with a list of patients registered for a transplant. This list will contain the average number of patients registered on each day of 2008, with the patients randomly selected from the pool of all those registered between 1 January 2005 and 31 December 2008. A pool of liver donors from 1 January 2005 to 31 December 2008 will be identified. Note that livers used for super-urgent patients will be excluded from the donor pool as they will remain with super-urgent patients under the proposed allocation scheme. Additionally, all paediatric donor livers that were transplanted into paediatric patients will be excluded, so too will livers retrieved and transplanted in the Republic of Ireland.

It will be assumed that the number of donors per day has a Poisson distribution with mean equal to the average daily number of donors in 2008. From 1 January 2007,

on each day, a random number of donors from an assumed Poisson distribution will be drawn from the donor pool. For each compatible person on the transplant list, their UKELD score will be simulated from the model for the slope of UKELD values described in Section 4.

Estimated expected lifetimes over 5 years are then obtained for each blood group compatible patient on the transplant list, using the models described in Section 2. Patients are then ranked by transplant benefit and the patient who is ranked highest is then assumed to have the transplant.

This patient is then removed from the transplant list but returned to the pool of potential registrants. The donor is also returned to the pool of potential donors. A new patient is then added to the transplant list.

This process continues for a two year period. The simulation is then repeated 100 times or more depending on the time taken and the resulting precision of the simulation based estimates.

Following this, average survival for transplanted patients can be estimated using the model for transplant survival. The characteristics of patients transplanted can also be determined (eg, proportion of males, proportion with ALD) and compared with proportions registered. The results can also be compared to the actual allocations over this period.

7 Possible refinements

1. Allow for a probability of declining an organ in the simulation process.
2. Simulate according to regional or centre pools of donors and potential recipients.
3. Allow for different types of censoring (non-informative and informative).
4. Include super-urgent registrations and transplants in the datasets for analysis.

8 References

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