NHS BLOOD AND TRANSPLANT

LIVER ADVISORY GROUP

SURVIVAL BASED CUSUM MONITORING - SUMMARY

1. BACKGROUND

1.1. NHSBT monitors short-term patient outcomes following organ transplantation through centre specific cumulative sum (CUSUM) analyses. These are undertaken monthly for liver transplantation and enable prompt detection of any changes in mortality rates, provide external assurance and enable centres to compare current outcomes with their own past performance to assist in internal auditing. CUSUM monitoring compares current outcome rates with an expected rate.

1.2 However, the current CUSUMs only monitor patient status (alive/dead) at 90 days post-transplant. It does not take into account the actual survival time post-transplant. This means that a death at 7 days post-transplant is treated the same as a death 89 days post-transplant. However, the hazard of death is likely to be higher immediately post-transplant and then decrease over time.

1.3 This paper presents changes in the CUSUM methodology which will incorporate the survival time post-transplant.

2. DATA AND METHODS

2.1 CUSUM charts monitor survival following first, NHS group 1, deceased donor liver only transplants performed in the UK. Patients who received a retransplant or a multi-organ transplant (for example a simultaneous liver and kidney transplant) are excluded from the CUSUM monitoring. Identical inclusion/exclusion criteria used in the currently implemented CUSUM charts will be used in the new survival based CUSUM charts.

2.2 The target time period will be 1 January 2012 to 31 December 2015 whilst the monitoring time period will be from 1 January 2016 for both adult and paediatric patients. This is identical to the revised periods for the currently implemented CUSUMs. Similar to the current CUSUM charts, the new survival based CUSUM charts will be run with a four month time lag post-transplant. For instance, CUSUM charts for transplants performed between 1 January 2016 and 31 May 2017 were produced in October 2017.

2.3 Missing values, for variables included in the risk-adjusted models, may occur in both the target building period and the monitoring period. One approach is to assign missing values to a particular risk group (e.g. low risk). Alternatively, missing values could be imputed using multiple imputation (MI) techniques. This approach is preferred for the target building period but not on a monthly basis for the monitoring period as charts would be produced for each centre, age group and urgency status for each of the 20 imputed datasets.

2.4 For the target building period, multiple imputation will be used to produce 20 imputed datasets. Cox proportional hazards regression modelling will be used to determine factors that affect 90-day survival for each of the 20 imputed datasets. Factors statistically significant for more than 10 datasets will be included in the final risk-adjusted model used in the survival based CUSUM charts.

2.5 For the monitoring period, the centre-specific modal or median value for the target building period will be used for missing values. For example, the median cold ischaemia time for centre A for the four year time period would be used for any missing cold ischaemia times at centre A. These values will be updated when the target building period will be updated and would not vary depending upon transplant year.

2.6 Two different CUSUM charts are currently produced and sent to centres on a monthly basis. Both charts are unadjusted and are plotted by transplant number. The first chart is the observed (O) minus expected (E) chart using the centre-specific expected mortality rate. The observed value used in the chart is a binary value determined by whether the patient is alive or dead at 90 days post-transplant. The second chart is the tabular CUSUM which summarises the extent to which the outcome is consistent with the expected rate.

2.7 Two charts will also be produced for the new survival based CUSUMs and **Figure 1** shows an example of the new charts. The new charts will be plotted against time post-transplant rather than transplant number. The first is also an O-E chart similar to the first chart currently produced. The expected rate, however, is the expected number of deaths that occur on a particular day post-transplant using the cumulative hazard function obtained from a risk-adjusted Cox proportional hazards regression model rather than the expected mortality rate. The observed value will be the observed number of patient deaths on the particular day.

2.8 While the O-E chart is useful for providing a general picture of a centres performance, it does not indicate when a centre should be concerned and possibly take action. The one-sided CUSUM chart, similar to the tabular CUSUM chart, can be used to detect changes in the underlying event rate. This chart will also be risk-adjusted and use the observed and expected number of deaths on a particular day post-transplant for the same set of patients included in the O-E chart. The one-sided CUSUM performs a statistical comparison of the following

- 2.8.1 The likelihood of observing the centres outcomes if the centre is performing as expected
- 2.8.2 The likelihood of observing the outcomes if the centre truly had twice the expected event rate

2.9 Unlike the O-E chart, the one-sided CUSUM will be capped at zero. This prevents centres from building up “credit” during periods of good outcomes. A credit would create a situation in which a longer string of bad outcomes would be necessary to reach a predetermined threshold.

2.10 The current tabular CUSUM utilises a headstart which resets a charts value to half the chart threshold (e.g. if chart threshold was 2.5 then the tabular CUSUM value would reset to 1.25 after a signal). This will be explored for the new one-sided CUSUM.

2.11 Unlike the current CUSUMs, which used Average Run Lengths (ARL) to determine the threshold limit at which centres would be deemed to have signalled, 500 or 1000 simulations will be produced for each centre, age group and urgency status. The threshold chosen will be the 95th percentile of the simulated maximum one-sided CUSUM values.

2.12 **Table 1** shows the factors considered in the analysis of factors affecting 90 day survival. Preliminary analysis identified the following factors as statistically significant

2.12.1 Organ appearance, lifestyle activity, previous abdominal surgery, donor type, cold ischaemia time (hours), and recipient BMI for *adult elective* liver transplants

2.12.2 Ventilation status, serum potassium, previous abdominal surgery, grouped serum creatinine, organ appearance and cold ischaemia time for *adult super-urgent* transplants

2.13 During the analysis, NHSBT identified an issue with missing data for cold ischaemia time and this is being looked into by the transplant centres involved. This may lead to a change in the factors found to be statistically significant predictors of 90 day survival.

3. ACTIONS

3.1. Advice is required on the following

3.1.1. Are there any additional factors that should be considered in the risk-adjusted analysis?

3.1.2. How should missing values in the monitoring period be treated?

3.2. The new survival based CUSUM charts will initially be run in parallel with the currently implemented CUSUM charts for a period of six months while centres get familiar with the new charts. However, given that the new National Liver Offering Scheme is due to go live in early 2018, advice is required on when these new charts should be introduced.

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Statistics and Clinical Studies, NHSBT

NHS BLOOD AND TRANSPLANT

LIVER CORE GROUP

SURVIVAL BASED CUSUM MONITORING

1 BACKGROUND

1.2 NHSBT monitors short-term patient outcomes following organ transplantation through centre specific cumulative sum (CUSUM) analyses. These are undertaken monthly for liver transplantation and enable prompt detection of any changes in mortality rates, provide external assurance and enable centres to compare current outcomes with their own past performance to assist in internal auditing. CUSUM monitoring compares current outcome rates with an expected rate.

1.3 Currently, CUSUM charts monitor transplant outcome as a binary variable (alive/ dead) at 90 days post-transplant. This means that in order for a patient to be included in the CUSUMs they need to be alive at least 75 days post-transplant or died at any point post-transplant. Also, a death at 7 days post-transplant is treated the same as a death 90 days post-transplant. However, the hazard of death is likely to be higher immediately post-transplant and then decrease over time.

1.4 This paper presents changes in the CUSUM methodology which will incorporate the survival time post-transplant.

2 DATA AND METHODS

2.2 CUSUM charts monitor survival following first, NHS group 1, deceased donor liver only transplants performed in the UK. Patients who received a retransplant or a multi-organ transplant (for example a simultaneous liver and kidney transplant) are excluded from the CUSUM monitoring. Identical inclusion/exclusion criteria used in the currently implemented CUSUMs will be used in the new survival based CUSUMs.

2.3 Similar to the currently implemented CUSUMs, the new survival based CUSUMs will be run with a four month time lag post-transplant. For instance, CUSUM charts for transplants occurring between 1 January 2016 and 31 May 2017 would be produced in October 2017.

2.4 The currently implemented CUSUMs use the centre-specific 90-day mortality rate for a four year target period to calculate the decrease in the tabular CUSUM value for a monitoring period. The survival time post-transplant is not taken into account in the current CUSUMs, as simply the patient status (alive/dead) at 90 days post-transplant is used to calculate the centre-specific mortality rate.

2.5 In contrast, the survival based CUSUMs use the national data to estimate the risk-adjusted 90 day cumulative hazard function (H(t)) and parameter estimates using Cox proportional hazards regression modelling. The cumulative hazard function is the expected number of deaths to 90 days post-transplant. In order to ensure that the cumulative hazard function is representative of the current hazard function, the initial target time period will be 1 January 2012 to 31 December 2015 whilst the monitoring time period will begin at 1 January 2016. This will maintain consistency with the currently implemented CUSUMs.

3 RISK ADJUSTMENT

3.2 **Table 1** shows the factors used in the risk-adjusted models in the Annual organ specific report for adult elective and adult super-urgent liver transplants. Also shown are the factors included in the post-transplant survival part of the new liver offering scheme model. **Table A1** shows the demographics of paediatric registrations and transplants between 1 April 2016 and 31 March 2017. These factors will be considered when analysing factors that affect 90 day survival post-transplant.

3.3 Missing values, for variables included in the risk-adjusted models, may occur in both the target building period and the monitoring period. One approach is to assign missing values to a particular risk group (e.g. low risk). Alternatively, missing values could be imputed using multiple imputation (MI) techniques. This approach is preferred for the target building period but not on a monthly basis for the monitoring period as charts would be produced for each centre, age group and urgency status for each of the 20 imputed datasets.

3.4 For the target building period, the imputation model will include all variables considered in the analysis plus the outcome variables, survival time and censoring indicator. 20 imputations will be run with 50 burn-in iterations and Cox proportional hazards regression modelling will be used to determine factors that affect 90-day survival for each of the 20 imputed datasets. Factors statistically significant for more than 10 datasets will be included in the final risk-adjusted model.

3.5 The centre-specific modal or median value for the target building period will be used for missing values in the monitoring period. For example, the median cold ischaemia time for centre A for the four year time period would be used for any missing cold ischaemia times at centre A. These values will be updated when the target building period will be updated and would not vary depending upon transplant year.

3.6 During the analysis, NHSBT identified an issue with missing cold ischaemia time and this is being looked into by the transplant centres involved.

Table 1 Factors included in 2016 annual report risk-adjusted models and 5-year post-transplant survival section of new liver offering scheme

	Adult elective model in 2016 annual report	Adult super-urgent model in 2016 annual report	5-year post-transplant survival section of new liver offering scheme (adult elective)
RECIPIENT related factors			
Recipient sex	√	√	√
Recipient ethnicity	√	√	
Disease	√		√
HCV status	√	√	√
In-patient status pre-transplant	√	√	√
Ascites	√	√	√
Encephalopathy	√	√	√
Renal support pre-transplant	√	√	√
Previous abdominal surgery	√	√	√
Varices & shunt	√	√	
Life style activity	√	√	
Recipient age (linear)	√	√	√
BMI (linear)	√	√	
Serum bilirubin	√ (≤ 30, 31-50, 51-70, 71-90, ≥91)	√ (≤ 100, 101-200, 201-300, 301-400, ≥401)	√ (linear)
Serum creatinine	√ (≤ 70, 71-90, 91-110, 111-130, ≥131)	√ (≤ 100, 101-130, 131-160, 161-190, ≥191)	√ (linear)
Serum sodium (linear)	√	√	√
Serum potassium (linear)	√	√	√
INR (linear)	√	√	√
Serum albumin (linear)	√	√	√
Time on transplant list	√ (1 month increase)	√ (1 month increase)	√ (1 log unit increase)
Diabetes			√
Maximum AFP level			√ (only for cancer patients)
Maximum tumour size			√ (only for cancer patients)
Number of tumours			√ (only for cancer patients)
DONOR related factors			
Donor sex	√	√	
Donor ethnicity	√	√	
Donor cause of death	√	√	√
Donor history of diabetes	√	√	√
Donor type	√	√	√
Donor age (linear)	√	√	√
Donor BMI (linear)	√	√	√
TRANSPLANT related factors			
Graft appearance	√	√	
Cold ischaemia time (linear)	√	√	
ABO match	√	√	√
Graft type	√	√	√

3.7 Preliminary analysis for the target building period, where missing values were assigned the modal value, identified the following factors as statistically significant predictors of 90 day survival:

3.6.1 Organ appearance, lifestyle activity, previous abdominal surgery, donor type, cold ischaemia time (hours), and recipient BMI for *adult elective* liver transplants

3.6.2 Ventilation status, serum potassium, previous abdominal surgery, grouped serum creatinine, organ appearance and cold ischaemia time for *adult super-urgent* transplants

4 EXAMPLE OF NEW SURVIVAL BASED CHARTS

4.2 Two different CUSUM charts are currently produced and sent to centres on a monthly basis. Neither charts are risk-adjusted and both charts are plotted by transplant number. The first chart shows the observed (O) minus expected (E) chart using the expected mortality rate from the target building period. The observed value used in the chart is whether the patient is alive or dead at 90 days post-transplant. The second chart is the tabular CUSUM which summarises the extent to which the outcome is consistent with the expected rate.

4.3 Two charts will also be produced for the new survival based CUSUMs and **Figure 1** shows an example of the new charts. The new charts will be plotted against time post-transplant rather than transplant number. The first is also a O-E chart similar to first chart currently produced. The expected rate, however, is the expected number of deaths that occur on a particular day post-transplant using the risk-adjusted cumulative hazard function. The observed value used will be the observed number of patient deaths on the same day.

4.4 A centre experiencing patient deaths at a rate higher than expected will see their O-E chart trend upward while a centre who experience events at a rate lower than expected will see a downward trend. A centre whose programme is consistent with expectation will see that their O-E CUSUM chart will remain relatively stable over time.

4.5 The second chart is the one sided CUSUM, which is similar to the tabular CUSUM, and can be used to detect changes in the underlying event rate. This chart will also be risk-adjusted and use the observed and expected number of deaths on a particular day post-transplant for the same set of patients included in the O-E chart. The one-sided CUSUM performs a statistical comparison of the following

4.5.1 The likelihood of observing the centres outcomes if the centre is performing as expected

4.5.2 The likelihood of observing the outcomes if the centre truly had twice the expected event rate

4.6 Unlike the O-E chart, the one-sided CUSUM will be capped at zero. This prevents centres from building up “credit” during periods of good outcomes. A credit would create a situation in

which a longer string of bad outcomes would be necessary to reach a predetermined threshold.

4.7 The current tabular CUSUM utilises a headstart which resets a charts value to half the chart threshold (e.g. if chart threshold was 2.5 then headstart would reset the chart to 1.25 after a signal). This will be explored for the new one-sided CUSUM.

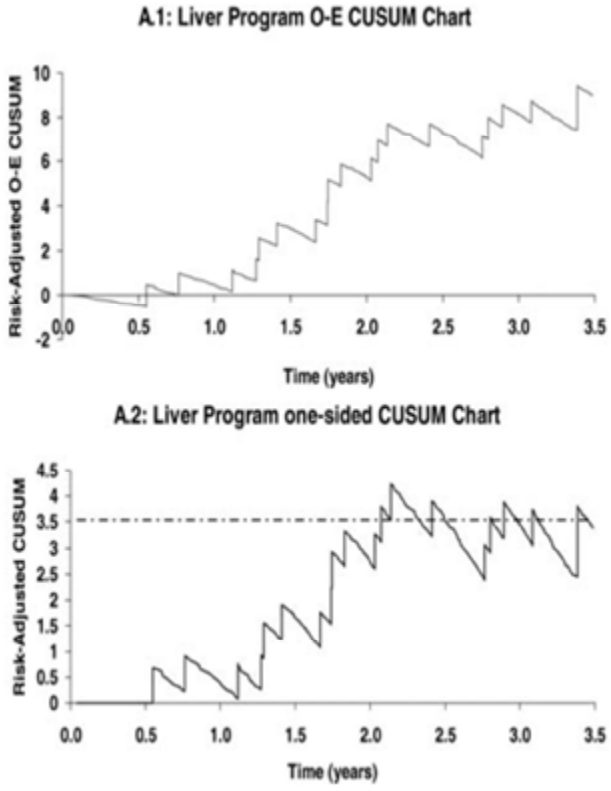
4.8 Unlike the current CUSUMs, simulations will be run to determine the threshold limit at which centres would be deemed to have signalled. Specifically, 500 or 1000 CUSUM charts will be simulated for each centre and transplant type assuming that the centre is performing as expected based on its daily expected event rate. For each of the simulated CUSUM charts, the highest point reached will be noted, yielding 500/1000 maximum values. The threshold is chosen to be the 95% percentile of the simulated maximum values.

4.9 Two risk-adjusted models will be analysed to determine whether there is any differences and the factors included will be:

4.9.1 Only factors found to be statistically significant

4.9.2 All factors included in the analysis

Figure 1 Example of new survival based CUSUMs



5. ACTIONS

5.1. Advice is required on the following

5.1.1. Are there any additional factors that should be considered in the risk-adjusted analysis?

5.1.2. How should missing values in the monitoring period be treated?

5.2. The new survival based CUSUM charts will initially be run in parallel with the currently implemented CUSUM charts for a period of six months while centres get familiar with the new charts. However, given that the new National Liver Offering Scheme is due to go live in early 2018, advice is required on when these new charts should be introduced.

Rhiannon Taylor and Elisa Allen **November 2017**

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Table A1 Demographic characteristics of paediatric registrations and deceased donor liver transplant recipients, 1 April 2016 - 31 March 2017

		Birmingham N (%)		King's College N (%)		Leeds N (%)		**TOTAL N (%)**	
		Registration	Transplant	Registration	Transplant	Registration	Transplant	**Registration**	**Transplant**
Number		39	20	52	41	17	15	**108**	**76 (100)**
Recip age years	<1	15 (38)	7 (35)	16 (31)	8 (20)	4 (24)	3 (20)	**35 (32)**	**18 (24)**
	1-4	11 (28)	7 (35)	14 (27)	20 (49)	6 (35)	6 (40)	**31 (29)**	**33 (43)**
	5-12	7 (18)	4 (20)	12 (23)	8 (20)	2 (12)	2 (13)	**21 (19)**	**14 (18)**
	13-16	6 (15)	2 (10)	10 (19)	5 (12)	5 (29)	4 (27)	**21 (19)**	**11 (15)**
Recipient sex	Male	18 (46)	9 (45)	28 (54)	24 (59)	9 (53)	7 (47)	**55 (51)**	**40 (53)**
	Female	21 (54)	11 (55)	24 (46)	17 (41)	8 (47)	8 (53)	**53 (49)**	**36 (47)**
Indication	Super Urgent	6 (15)	2 (10)	10 (19)	5 (12)	3 (18)	2 (13)	**19 (18)**	**9 (12)**
	Biliary Atresia	12 (31)	7 (35)	24 (46)	17 (41)	3 (18)	4 (27)	**39 (36)**	**28 (37)**
	Other Cholestatic	0 (0)	0	2 (4)	0	2 (12)	1 (7)	**4 (4)**	**1 (1)**
	Metabolic	4 (10)	2 (10)	3 (6)	3 (7)	2 (12)	1 (7)	**9 (8)**	**6 (8)**
	Other	17 (44)	9 (45)	13 (25)	16 (39)	7 (41)	7 (47)	**37 (34)**	**32 (42)**
Pre-transplant in-patient status	Out-patient	-	14 (70)	-	30 (73)	-	11 (73)	-	**55 (72)**
	In-patient	-	5 (25)	-	10 (24)	-	4 (27)	-	**19 (25)**
	Not reported	-	1 (5)	-	1 (2)	-	0	-	**2 (3)**
Pre-transplant renal support	No	-	18 (90)	-	32 (78)	-	15 (100)	-	**65 (86)**
	Yes	-	1 (5)	-	7 (17)	-	0	-	**8 (11)**
	Not reported	-	1 (5)	-	2 (5)	-	0	-	**3 (4)**
Ascites	Absence	-	7 (35)	-	36 (88)	-	13 (87)	-	**56 (74)**
	Presence	-	12 (60)	-	3 (7)	-	2 (13)	-	**17 (22)**
	Not reported	-	1 (5)	-	2 (5)	-	0	-	**3 (4)**
Previous abdominal surgery	No	15 (38)	10 (50)	17 (33)	24 (59)	7 (41)	8 (53)	**39 (36)**	**42 (55)**
	Yes	18 (46)	9 (45)	25 (48)	15 (37)	7 (41)	6 (40)	**50 (46)**	**30 (40)**
	Not reported	0 (0)	1 (5)	0 (0)	2 (5)	0 (0)	1 (7)	**0 (0)**	**4 (5)**
	Not collected for super-urgent txs	6 (15)	2 (10)	10 (19)	5 (12)	3 (18)	2 (13)	**19 (18)**	**9 (12)**

Table A1 Demographic characteristics of paediatric registrations and deceased donor liver transplant recipients, 1 April 2016 - 31 March 2017

		Birmingham N (%)		King's College N (%)		Leeds N (%)		**TOTAL N (%)**	
		Registration	Transplant	Registration	Transplant	Registration	Transplant	**Registration**	**Transplant**
INR	<=1.0	13 (33)	2 (10)	9 (17)	3 (7)	8 (47)	7 (47)	**30 (28)**	**12 (16)**
	1.1-1.5	18 (46)	9 (45)	27 (52)	17 (41)	5 (29)	4 (27)	**50 (46)**	**30 (40)**
	1.6-3.0	4 (10)	5 (25)	8 (15)	17 (41)	2 (12)	2 (13)	**14 (13)**	**24 (32)**
	>3.0	1 (3)	3 (15)	8 (15)	3 (7)	2 (12)	2 (13)	**11 (10)**	**8 (11)**
	Not reported	3 (8)	1 (5)	0 (0)	1 (2)	0 (0)	0 (0)	**3 (3)**	**2 (3)**
Serum sodium mmol/l	<135	9 (23)	5 (25)	7 (13)	2 (5)	1 (6)	1 (7)	**17 (16)**	**8 (11)**
	>=135	30 (77)	14 (70)	45 (87)	38 (93)	16 (94)	13 (87)	**91 (84)**	**65 (86)**
	Not reported	0 (0)	1 (5)	0 (0)	1 (2)	0 (0)	1 (7)	**0 (0)**	**3 (4)**
Donor age years	<5	-	0 (0)	-	3 (7)	-	0 (0)	-	**3 (4)**
	5-16	-	6 (30)	-	6 (15)	-	4 (27)	-	**16 (21)**
	17-30	-	10 (50)	-	18 (44)	-	7 (47)	-	**35 (46)**
	>=31	-	4 (20)	-	14 (34)	-	4 (27)	-	**22 (29)**
Donor sex	Male	-	16 (80)	-	28 (68)	-	9 (60)	-	**53 (70)**
	Female	-	4 (20)	-	13 (32)	-	6 (40)	-	**23 (30)**
Donor type	Donor after brain death	-	17 (85)	-	39 (95)	-	15 (100)	-	**71 (93)**
	Donor after cardiac death	-	3 (15)	-	2 (5)	-	0 (0)	-	**5 (7)**
Graft appearance	Normal	-	18 (90)	-	23 (56)	-	15 (100)	-	**56 (74)**
	Not reported	-	2 (10)	-	18 (44)	-	0 (0)	-	**20 (26)**
Graft type	Whole	-	3 (15)	-	8 (20)	-	4 (27)	-	**15 (20)**
	Segmental	-	17 (85)	-	33 (80)	-	11 (73)	-	**61 (80)**
Urgency Status	Elective	33 (85)	18 (90)	42 (81)	36 (88)	14 (82)	13 (87)	**89 (82)**	**67 (88)**
	Super Urgent	6 (15)	2 (10)	10 (19)	5 (12)	3 (18)	2 (13)	**19 (18)**	**9 (12)**